Refractory Status Epilepticus – Classification, Mechanisms, and Treatment

Eugen Trinka
Department of Neurology, Christian Doppler Medical Centre,
Paracelsus Medical University and
Centre for Cognitive Neuroscience, Salzburg, Austria

at.linkedin.com/pub/eugen-trinka/a7/6a0/a08
https://www.researchgate.net/profile/Eugen_Trinka

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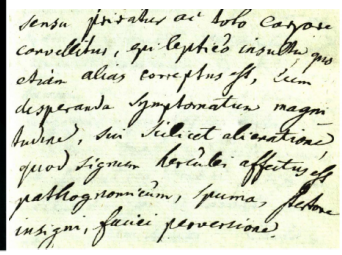
Historical Note

The demise of Archbishop Wolf Dietrich – A historical note on a fatal status epilepticus documented at Salzburg in 1617

Gudrun Kalss [a,b,*], Julia Höfler [a,b], Alexandra Rohracher [a,b], Ildiko Deak [a,b], Judith Dobesberger [a,b], Giorgi Kuchukhidze [a,b,c], Markus Leitinger [a,b], Kathrin Ogris [d], Mark Mc Coy [e], Eugen Trinka [a,b]

[a] Department of Neurology, Christian Doppler Medical Centre, Paracelsus Medical University Salzburg, Ignaz Harrer Strasse 79, 5020 Salzburg, Austria
[b] Centre for Cognitive Neuroscience, Ignaz Harrer Strasse 79, 5020 Salzburg, Austria
[c] Department of Neurology, Medical University of Innsbruck, Innrain 52, Christoph-Probst-Platz, 6020 Innsbruck, Austria
[d] Department of Legal Medicine, Medical University of Graz, Universitätsplatz 4/2, 8010 Graz, Austria
[e] Division of Neuroradiology, Christian Doppler Medical Centre, Paracelsus Medical University Salzburg, Ignaz Harrer Strasse 79, 5020 Salzburg, Austria



"...he loses consciousness. His whole body is jerked by an epileptic seizure, as he suffered from before. The symptoms are of such desperate magnitude, namely unconsciousness, salivation, breathing in a stertorously way and distortion of his face, which are pathognomonic for the disease of Hercules."

Historical Vignette

Wolf Dietrich of Raitenau ruled the archiepiscopal Salzburg from 1587 to 1611.

Died on January 16th 1617

first well-documented left hemispheric stroke in winter 1604/05 followed later by a right sided stroke:

„leva corporis pars iam pridem simili ex apoplectico assultu in paralysin resoluta"

"epileptico insultu quo etiam alias correptus est"

Kalss G, et al. Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.024

Epidemiology of Status Epilepticus

- Incidence 10-41/100.000/a → one of the most common neurological emergencies[1]
- 70.000 - 300.000 patients in Europe
- ≈20% mortality[2]
- < 50% with preexisting epilepsy[1,2]
  - Low AED level
- 50% acute symptomatic SE[1,2]
  - Cerebrovascular diseases, traumatic brain injury, encephalitis, meningitis, alcohol related, metabolic

1 Coeytaux et al. Neurology 2000; DeLorenzo et al. Neurology 1996; Hesdorffer et al. Neurology 1998; Knake et al. Epilepsia 2001; Vignatelli et al. Epilepsia 2003
2 Logroscino et al. Epilepsia 1997; 2006; Shorvon 1994

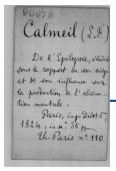
Epidemiology of Status Epilepticus

	[1]Richmond Virginia, USA	[2]Rochester, Minn., USA	[3]West-switzerland	[4]Hessen, Germany	[5]Bologna, Italy
Year	1989-1991	1965-1984	1997-1998**	1997-1999	1999-2000
N / Population	166 / 202,774	199 / 1,090,055	172 / 1,735,420	150 / 743,285	44 / 336,876
Incidence/ 100,000/yr	**61***	**18.3***	**10,3***	**17.1**	**10.7**
Female:male	1:1.2	1:1.9	1:1.7	1:1.9	1:0.84
Hx of epilepsy	**42%**	**44%**	**32.8%**	**50%**	**39%**
Simple focal	23%	39%	18.1%	13.3%	9%
Complex focal	3%		26.7%	43.3%	19%
Absence	1%	3.5%	3.5%	6.0%	2%
Myoclonic	1%	9.5%			26%
Tonic clonic	70%	48%	33.1%	33.3%	50%

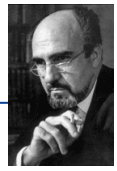
1 DeLorenzo et al. Neurology 1995; 2 Hesdorffer et al. Neurology 1998; 3 Coeytaux et al. Neurology 2000; 4 Knake et al. Epilepsia 2001; 5 Vignatelli et al. Epilepsia 2003

Agenda

- Definition and classification of status epilepticus
- Causes and mechanisms
- Staged Treatment approach
  - Refractory Status epilepticus
  - Super-refractory Status epilepticus
- Prognosis
- Concluding remarks



Definition of Status Epilepticus



Traditional classification:

• There were as many types of status as there were types of epileptic seizures (draft 1962; final 1967)

• SE classification mirrored the seizure classification (1964, final 1970)

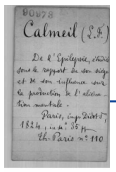
„a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur“ ILAE 1981[1]

Majority of GTCS < 2-3 min[3,6]

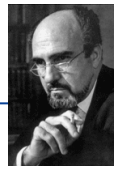
Operational definition: 5min[4,5]

…“Mechanistically, SE represents the failure of the natural homeostatic seizure-suppressing mechanisms for seizure termination.”…[2]

1: Commission on Classification ILAE, Epilepsia 1981; 2 Engel et al. Epilepsia 2006; 3 Theodore et al. 1994; 4 Lowenstein et al. 1999; 5 Trinka et al. 2015; 6: Dobesberger et al. 2015



Definition of Non Convulsive Status Epilepticus



Traditional classification:

- There were as many types of status as there were types of epileptic seizures (draft 1962; final 1967)
- SE classification mirrored the seizure classification (draft 1964, final 1970)

„enduring epileptic condition with reduced/altered consciousness, behavioral and vegetative abnormalities or merely subjective symptoms, without major convulsive movements“

NCSE Definition 30 min

NCSE Definition 10 min[5]

…“Mechanistically, SE represents the failure of the natural homeostatic seizure-suppressing mechanisms for seizure termination.”…[2]

1: Commission on Classification ILAE, Epilepsia 1981; 2 Engel et al. Epilepsia 2006; 3 Theodore et al. 1994; 4 Lowenstein et al. 1999; 5 Trinka et al. 2015

Definition of Status Epilepticus

Status epilepticus is a condition resulting either from the *failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms*, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizure

Trinka et al. Epilepsia 2015 in press

Definition of Status Epilepticus

Status epilepticus is a condition resulting either from the *failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms*, which lead to **abnormally, prolonged seizures** (**after time point t1**). It is a condition, which can have **long-term consequences (after time point t2)**, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizure

Conceptual (="mechanistic") definition

2 Operational dimensions:
- → length of seizure (t_1)
- → time (t_2) to long term consequences

Trinka et al. Epilepsia 2015 in press

Type of SE	Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity	Time (t2), beyond which long term consequences are increasingly likely (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic clonic SE	5 minutes	<30 minutes
SE with impairment of consciousness	10 minutes	30-60 minutes*
Absence status epilepticus	2 minutes*	unknown*
Implications to treatment	**Time point 1 determines the earliest time when treatment should be considered or started**	**Time point 2 determines the time at which status should be controlled to prevent long term consequences**

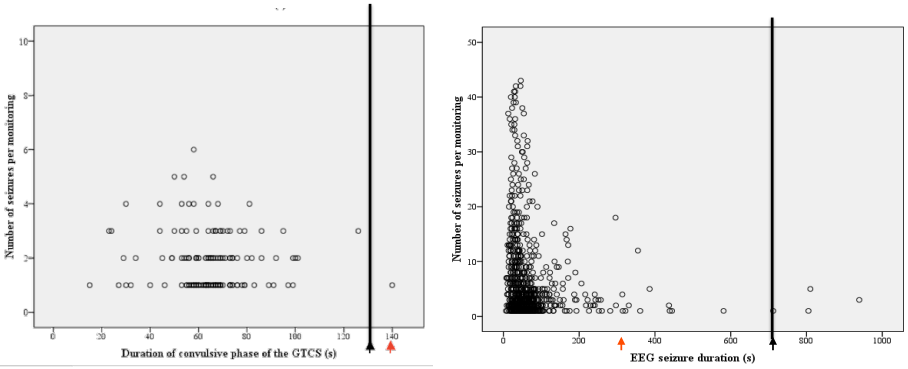
* Best available evidence, but insufficient data to give a definite timepoint

Trinka et al. Epilepsia 2015 in press

How long do seizures last in monitoring units?

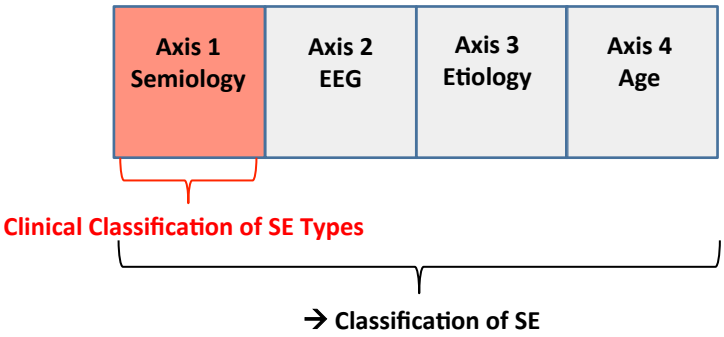
Mean seizure duration +4 SD

Cumulative 99% seizure duration of focal complex seizures



1: Dobesberger, Trinka and Ristic Epilepsy and Behavior 2015

Classification of SE



Trinka et al. Epilepsia 2015 in press

Axis 1 = semiology
Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

A) With prominent motor symptoms

B) Without prominent motor symptoms (i.e. NCSE)

Trinka et al. Epilepsia 2015 in press

Axis 1 = semiology
Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

A) With prominent motor symptoms

- **Convulsive SE (syn.: tonic clonic SE, CSE)**
- **Myoclonic SE** *(prominent epileptic myoclonic jerks)*
- **Focal motor** *(including EPC)*
- **Tonic SE**
- **Hyperkinetic SE**

B) Without prominent motor symptoms (i.e. NCSE)

Trinka et al. Epilepsia 2015 in press

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- **Hyperkinetic SE**

B) Without prominent motor symptoms (i.e. NCSE)

- **NCSE with coma**
- **NCSE without coma**
  - **Generalised**
  - **Focal**

Trinka et al. Epilepsia 2015 in press

Axis 1 = semiology
Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

A) With prominent motor symptoms

- **Convulsive SE (syn.: tonic clonic SE, CSE)**
  - **Generalised convulsive**
  - **Focal onset evolving into bilateral convulsive SE**
  - **Unknown whether focal or generalised**
- **Myoclonic SE**
  - **With coma**
  - **Without coma**
- **Focal motor**
  - **Repeated focal motor seizures (Jacksonian)**
  - **Epilepsia Partialis Continua (EPC)**
  - **Adversive status**
  - **Oculoclonic status**
  - **Ictal paresis**
- **Tonic SE**
- **Hyperkinetic SE**

Trinka et al. Epilepsia 2015 in press

Axis 1 = semiology
Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

B) Without prominent motor symptoms (i.e. NCSE)

- **NCSE with coma**
- **NCSE without coma**
  - **Generalised**
    - **Typical absence status**
    - **Atypical absence status**
    - **Myoclonic absence status**
  - **Focal**
    - **Without impaired consciousness (Aura continua)**
      - (With autonomic*, sensory symptoms, visual, olfactory, gustatory, emotional, auditory symptoms
    - **Aphasic SE**
    - **With impaired consciousness**
  - **Unknown**
    - **Autonomic SE***

* Differentiation between 2.b.a and 2.c.a has to be discussed

Trinka et al. Epilepsia 2015 in press

Axis 1 = semiology
Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

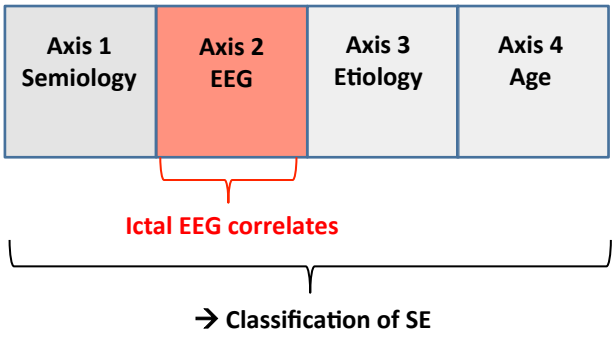
Currently indeterminate conditions**

- **Epileptic encephalopathies**
- **Coma with epileptiform EEG patterns**
- **Behavioural disturbance (e.g psychosis) in patients with epilepsy**
- **Acute confusional states (e.g delirium) with epileptiform EEG patterns**

**= Boundary syndromes

Trinka et al. Epilepsia 2015 in press

Classification of SE



Trinka et al. Epilepsia 2015 in press

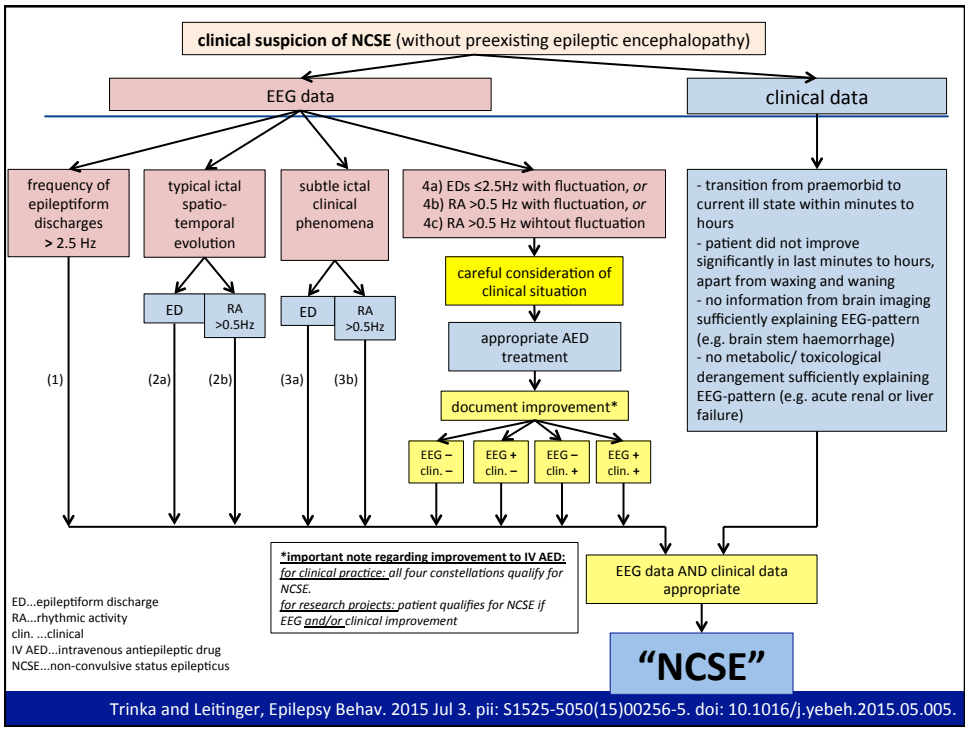
Proposed EEG Criteria for NCSE –

For patients without epileptic encephalopathies:

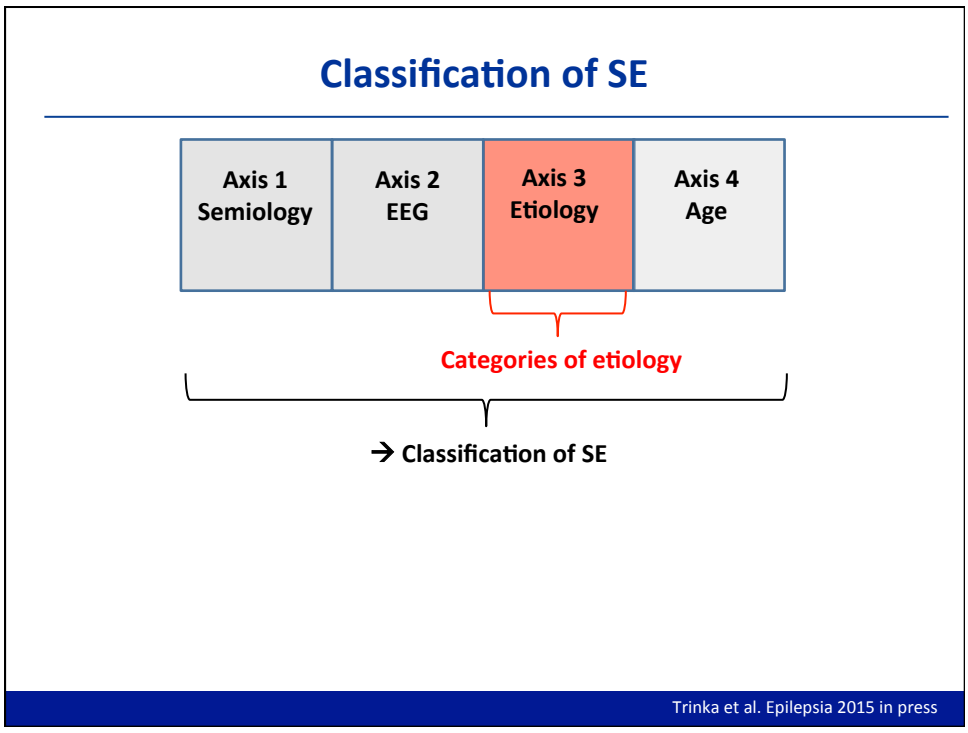
- EDs > 2.5 Hz, *or*
- EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) AND one of the following:
  - EEG and clinical improvement after IV AED*, *or*
  - Subtle clinical ictal phenomena, *or*
  - Typical spatiotemporal evolution**

If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered **possible NCSE.*
***Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).*

Beniczky et al. Epilepsia 2013



Trinka and Leitinger, Epilepsy Behav. 2015 Jul 3. pii: S1525-5050(15)00256-5. doi: 10.1016/j.yebeh.2015.05.005.



Trinka et al. Epilepsia 2015 in press

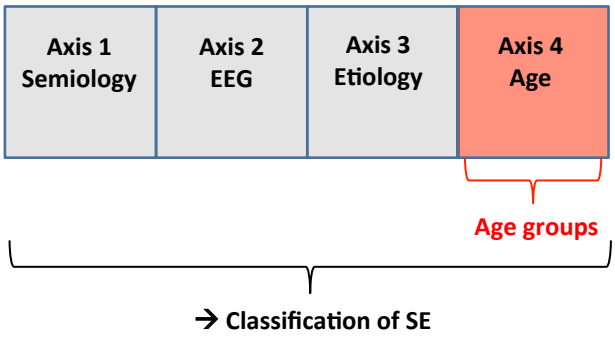
Classification of SE: Axis 3 Etiology

1. **Known** (= **symptomatic)**
   a) Acute (e.g.: stroke, intoxication, malaria, encephalitis, etc.)
   b) Remote (e.g. posttraumatic, postencephalitic, poststroke, etc.)
   c) Progressive (e.g. glioblastoma, Lafora´s disease and other PMEs)
   d) SE in defined electroclinical syndromes
2. **Unknown** (= **cryptogenic**)[1]

1: Synonymous translations germ.: ungeklärt; french: xxx, span.: yyy; ital.: zzz, russ.: aaa ...)

Trinka et al. Epilepsia 2015 in press

Classification of SE



Trinka et al. Epilepsia 2015 in press

Age Related Disorders and Electroclinical Syndromes with SE

1. **SE occurring in the neonatal and infantile epilepsy syndromes**
   a) Tonic Status in Ohtahara Syndrome
   b) Myoclonic status in Dravet´s syndrome
   c) Febrile SE
      i. With bilateral motor symptoms
      ii. With unilateral motor symptoms
2. **SE occurring predominately in childhood and adolescence**
   a) NCSE in Early-onset Childhood Occipital Epilepsy (Panayiotopoulos syndrome)
   b) NCSE in childhood epileptic encephalopathies (e.g., myoclonic-astatic epilepsy, Ring chromosome 20, Angelman syndrome → see appendix)
   c) Tonic status in Lennox Gastaut Syndrome
   d) Myoclonic Status in Down Syndrome
   e) Absence Status in Juvenile Absence Epilepsy
   f) Myoclonic Status in Juvenile Myoclonic Epilepsy
   g) Myoclonic Status in Progressive Myoclonus Epilepsies
   h) FIRES
3. **SE occurring only in adults and elderly**
   a) De Novo (or relapsing) absence status of later life

Trinka et al. *Epilepsia* 2015 in press

Agenda

- Definition and classification of status epilepticus
- Causes and mechanisms
- Staged Treatment approach
  - Refractory Status epilepticus
  - Super-refractory Status epilepticus
- Prognosis
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Etiology of Status epilepticus

Table 2. Major Etiologies of SE by Population-Based Study[a]

Variable	Patients, %						
	Richmond, Virginia[3b]	Rochester, Minnesota[4]	French-Speaking Switzerland[5]	Hessen, Germany[6]	California[7]	Bologna, Italy[8]	London, United Kingdom[9c]
Low AED levels	21 (P)/34 (A)	1	8.1[d]	8.7	3.9	NA	0.5
CNS infections	52 (P)/5 (A)	8.5	NA	0	0.6	NA	10.2
Febrile	NA	8	14.9[e]	0	2.5	NA	32
Cerebrovascular disease	10 (P)/22 (A)	19.1	30.5[f]	66.7	12.4	41	0.5
Alcohol abuse	13 (A)	NA	NA	8.7	8.1	7	0
Trauma	3 (A)	4.5	NA	7.3	0.4	10	1.5
CNS tumors	7 (A)	NA	NA	12	1.8	5	NA
Metabolic disturbance	5 (P)/15 (A)	3.5	NA	8.7	8.7	24[g]	3
Degenerative brain disease/ CNS anomalies	38 (P)/25 (A)	5.5	NA	26.7	13.3	10	32
Medication induced/overdose	2 (P)/3 (A)	2	NA	10.7	NA	NA	1
Anoxia/hypoxia	5 (A) (anoxia) 5(P)/ 13 (A) (hypoxia)	10	Excluded	NA	8	9.1	0.5
Cryptogenic	5 (P)/3 (A)	17.5	8.7	8.7	NA	11	11.7

1 Neligan et al. Arch Neurol 2010

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CNS infections	52 (P)/5 (A)	8.5	NA	0	0.6	NA	10.2
Febrile	NA	8	14.9[e]	0	2.5	NA	32
Cerebrovascular disease	10 (P)/22 (A)	19.1	30.5[f]	66.7	12.4	41	0.5
Alcohol abuse	13 (A)	NA	NA	8.7	8.1	7	0
Trauma	3 (A)	4.5	NA	7.3	0.4	10	1.5
CNS tumors	7 (A)	NA	NA	12	1.8	5	NA
Metabolic disturbance	5 (P)/15 (A)	3.5	NA	8.7	8.7	24[g]	3
Degenerative brain disease/ CNS anomalies	38 (P)/25 (A)	5.5	NA	26.7	13.3	10	32
Medication induced/overdose	2 (P)/3 (A)	2	NA	10.7	NA	NA	1
Anoxia/hypoxia	5 (A) (anoxia) 5(P)/ 13 (A) (hypoxia)	10	Excluded	NA	8	9.1	0.5
Cryptogenic	5 (P)/3 (A)	17.5	8.7	8.7	NA	11	11.7

1 Neligan et al. Arch Neurol 2010

Etiology of Status epilepticus

Table 3. Studies of Status Epilepticus in the Developing World

	Nigeria[13]	Trinidad[14]	Brazil[15]	Tunisia[16]	India[17]	Senegal[18]	Thailand[19]	Iran[20]	Congo[21]	Kenya[22]	Ethiopia[23]	China[24]
Study design	R	R	P	R	P	R	R	R	R	R	R	R/P
Study years or duration	10 y	18 mo	1989-1993	1990-1997	1994-1996	1988-1998	1981-2000	1999-2004	1998-2003	2002-2003	1997-2007	1996-2007
Patients, No.	41	41	111	139	85	697	32	135	607	388[a]	119	220
History of seizures, %	NA	NA	59.4	10	20	9.9	75	37	14.5	30.8	38.7	50
Etiology, %												
Febrile	NA	5	5.4	41	NA	8.6	0	51.1	NA	NA	NA	NA
AED noncompliance	NA	NA	18.9	10	20	9.9	9.4	28.2	3.8	5.9	17.6	15.5
CNS infection	41.5	15[b]	10.8	18.7	28	67	65.6	7.4	74.5[c]	8.0[d]	36.1	32.7
Metabolic disorders	34.1	NA	10.8	10.1	11	4.3	0	2.9	NA	NA	13.4	11.4[e]
Stroke	14.6	NA	9.9	5.8	15	8	0	0	NA	NA	12.6	10.9
Progressive symptomatic, %	9.8 frontal lobe tumors	NA	2.7	7	NA	1.2	3.1	0	NA	NA	10.9	NA
Remote symptomatic, %	NA	51	NA	6	7	NA	0	0	NA	NA	NA	NA
Idiopathic, %	NA	29	25.3	6	19	NA	18.8	8.9	NA	NA	16.8	7.7[f]
Mortality, %	100	0	19.8	15.8	10.5	24.8	6.3	12.6	26.5	15.2	20.2	15.9
Morbidity, %	NA	4.9	NA	36	NA	13.6	56.3, 66.7 severe neuro-logic deficit	27.3	2.9	11.9	3.4	NA
Inclusion criteria	All-ages postmortem study	All ages; 51% aged <10 y	All ages	Study in infants, mean age of 11 mo	All ages; mean age, 33 y	All ages; 61% aged <10 y	Pediatric study, mean age of 6.5y	Pediatric study	Pediatric study	Pediatric study	Children aged <13 y excluded	All ages; 12% aged <16 y

1 Neligan et al. Arch Neurol 2010

Etiology of Status epilepticus

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History of seizures, %	NA	NA	59.4	10	20	9.9	75	37	14.5	30.8	38.7	50
Etiology, %												
Febrile	NA	5	5.4	41	NA	8.6	0	51.1	NA	NA	NA	NA
AED noncompliance	NA	NA	18.9	10	20	9.9	9.4	28.2	3.8	5.9	17.6	15.5
CNS infection	41.5	15[b]	10.8	18.7	28	67	65.6	7.4	74.5[c]	8.0[d]	36.1	32.7
Metabolic disorders	34.1	NA	10.8	10.1	11	4.3	0	2.9	NA	NA	13.4	11.4[e]
Stroke	14.6	NA	9.9	5.8	15	8	0	0	NA	NA	12.6	10.9
Progressive symptomatic, %	9.8 frontal lobe tumors	NA	2.7	7	NA	1.2	3.1	0	NA	NA	10.9	NA
Remote symptomatic, %	NA	51	NA	6	7	NA	0	0	NA	NA	NA	NA
Idiopathic, %	NA	29	25.3	6	19	NA	18.8	8.9	NA	NA	16.8	7.7[f]
Mortality, %	100	0	19.8	15.8	10.5	24.8	6.3	12.6	26.5	15.2	20.2	15.9
Morbidity, %	NA	4.9	NA	36	NA	13.6	56.3, 66.7 severe neuro-logic deficit	27.3	2.9	11.9	3.4	NA
Inclusion criteria	All-ages postmortem study	All ages; 51% aged <10 y	All ages	Study in infants, mean age of 11 mo	All ages; mean age, 33 y	All ages; 61% aged <10 y	Pediatric study, mean age of 6.5y	Pediatric study	Pediatric study	Pediatric study	Children aged <13 y excluded	All ages; 12% aged <16 y

1 Neligan et al. Arch Neurol 2010

Etiology and Mortality of Status epilepticus

Table 4. Approximate Frequency and Mortality of SE of Different Etiologies[a]

	Proportion of Cases of SE, %	Associated Acute Mortality in Patients With SE, %
Drug reduction/withdrawal, poor compliance, or low AED levels	10-20	0-10
Cerebrovascular disease	10-40	20-60
Metabolic disorders	5-15	10-35
Acute CNS infections[b]	0-10	0-30
Anoxia	5-10	60-100
Alcohol abuse	5-15	0-10
Head trauma	0-10	0-25
Drug overdose/toxicity	0-10	10-25
Brain tumors	0-10	0-20
Cryptogenic/idiopathic	5-15	5-20

1 Neligan et al. Arch Neurol 2010

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Brain tumors	0-10	0-20
Cryptogenic/idiopathic	5-15	5-20

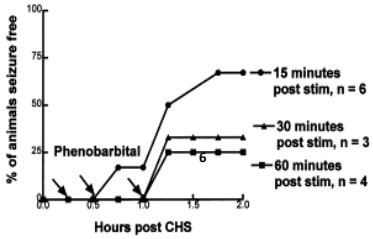
1 Neligan et al. Arch Neurol 2010

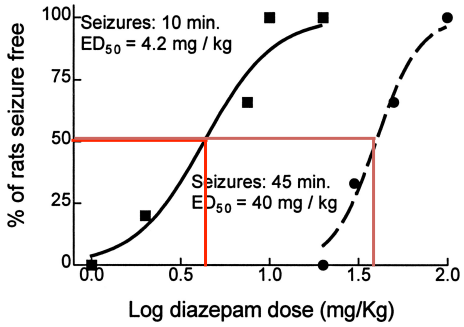
- Immunological disorders
  - Limbic encephalitis
  - Paraneoplastic encephalitis
  - Hashimoto encephalopathy
  - Anti-NMDA Encephalitis
- Mitochondrial Disorders
  - POLG1 Mutations
  - MELAS
- Rare infectious diseases
  - Cat Scratch disease
  - HIV and HIV related disease
- JCD
- Genetic disorders:
  - Ring Chromosome 20
  - Angelman Syndrome
- Porphyria
- Drugs/toxins
- Antiepileptic drugs
- Antimicrobials
- Chemotherapeutic agents
- Organophosphates
- …….

1 Tan et al. Epilepsy Research 2010

Self-sustaining status epilepticus[1-6]

- Chemical stimulation[1]
- Electical stimulation
  - Hippocampus[2]
  - Amygdala[3]
  - Perforant path[4]





Rapid seizure-induced loss of BDZ and Zn^{++} sensitivity of hippocampal GABAergic neurons[5]

Li-pilocarpin model rats

1. Buterbaugh GG et al. Exp Neurol 1986; 94:91-102; Morisette et al. Exp Neurol 1986; 2. Lothman EW et al. Epilepsy Res 1990; 6:110-8; Vicedomini JP and Nadler JV Exp Neurol 1987;96:681-91; van Vliet EA et al. Exp Neurol 2004; 187:367-793. Pitkanen A et al. Epilepsy Res 1998;32:233-53; 4. Mazarati AM et al. Brain Res 1998;801:251-3; 5. Kapur J and Macdonald RL J Neurosci 1997;17:7532-40; 6. Borris DJ et al. Epilepsy Res 2000;42:117-22

Receptor trafficking hypothesis

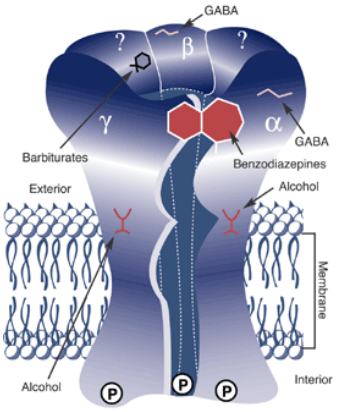


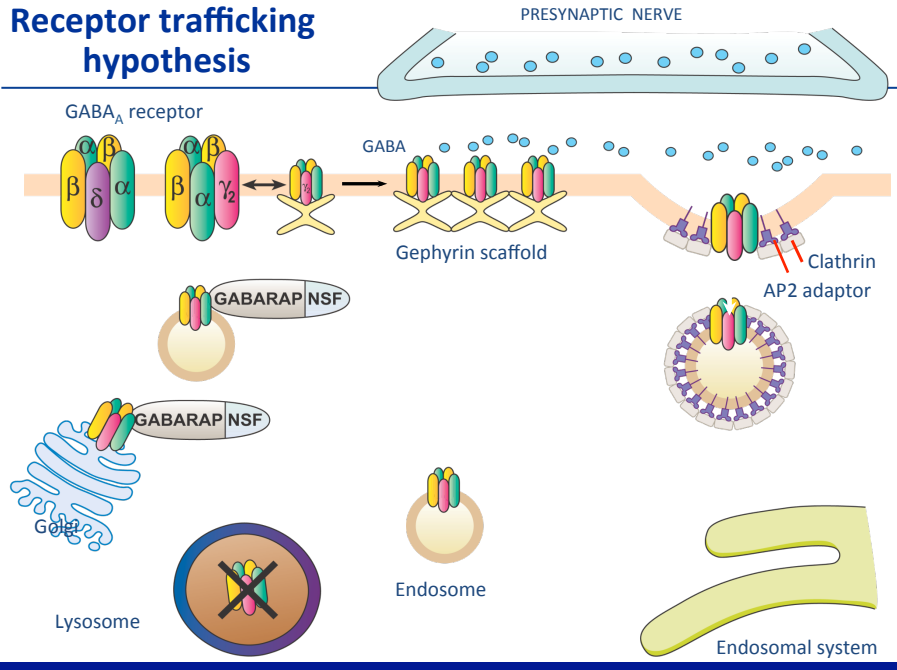
Table 1. Changes in the expression of $GABA_A$ receptor subunits in animal models of status epilepticus

	Kainic acid-induced status epilepticus			Electrically induced status epilepticus	
	12 h (*mRNA*) (Tsunashima et al., 1997)	7–30 d	30 d (*IR*) (Schwarzer et al., 1997)	24 h	7–30 d (*mRNA*) (Nishimura et al., 2005)
α_1	++	+	++	++	+
α_2	–	=	++	(–)	(+)
α_3	–	(+)	=	nd	nd
α_4	+	(+)	+	+	++
α_5	– –	–	±	–	(–)
β_1	+	+	±	+	+
β_2	±	++	++	++	++
β_3	(–)	(+)	++	+	(+)
γ_2	(–)	=	+	(+)	(+)
δ	–	–	–	– –	–

++, >150%; +, >115–150%; (+) 105–115%; =, 96–104%; (–), 91–95%; –, 50–80%; – –, <50% of controls.
Shaded values indicate statistical significance at $p < 0.05$ level or higher. nd, not determined.

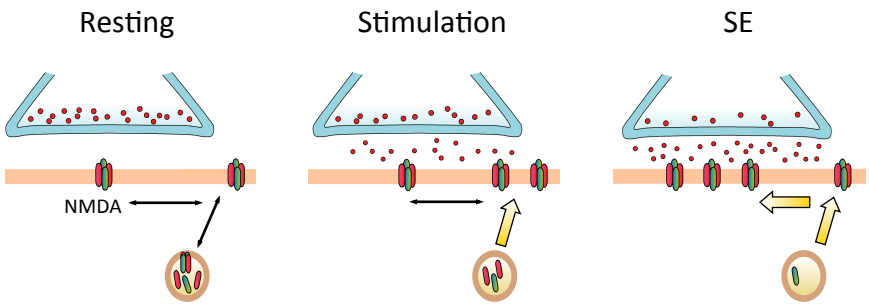
1. Mihic SJ and Harris RA. Alcohol Health & Research World 1997;21:127-31 2. Sperk G. Epilepsia 2007;48 Suppl 8:11-13

Receptor trafficking hypothesis

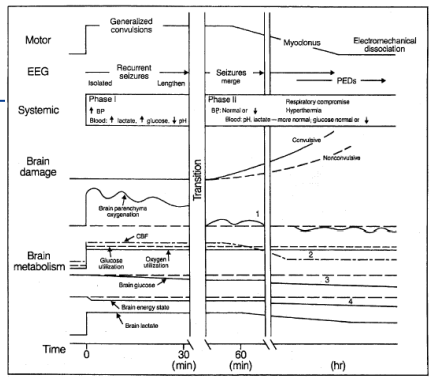


Adapted from Chen & Wasterlain, 2006 and Moss, Kittler and others with friendly permission of Claude Wasterlain

NMDA synapses

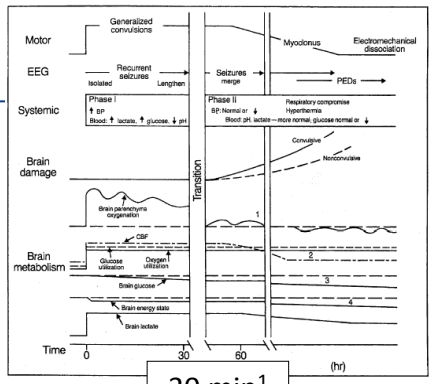


Adapted from Chen & Wasterlain Lancet Neurol 2006;5:246-56



Trousseau, 1867: "In the status epilepticus, when the convulsive condition is almost continuous, something special takes place which requires an explanation"

1. Lothman E. Neurology 1990;40 Suppl 2:13-23; 2. Krauss (AAN) Epilepsia 2009, 3. Chapell AS et al. 2002;58:1680-2;
4. Chen JW and Wasterlain CG Lancet Neurology 2006;5:246-56



30 min[1]

GABAergeic AEDs in the early phase of SE:

BDZ, PB

Early treatmnent with 2 AEDs with different modes of action?[4,5]

After GABAergic failure and maladaptive changes:

AntiGLUergeic AEDs[6]: KET[8], GYKI 52466[7], NS-1209[6] , PER[2], TAL[3], BGG492

AEDs with other modes of action: LEV, LCM, PHT, VPA

1: Lothman Neurology 1990; 2: Hanada et al. Epilepsia, 52(7):1331–1340, 2011, 3: Chapell et al. 2002 ; 4: Chen and Wasterlain Lancet Neurology 2006; 5: Wasterlain et al. Epilepsia 2013; 6: Kapur and Trinka Epilepsy Currents 2014 submitted; 7: Fritsch et al. Epilepsia 2010; Höfler et al. Epilepsia suppl 2013

Clinical course of convulsive status epilepticus

Stage 1	Early phase Premonitory SE, impending SE	5-10 min
Stage 2	Established SE	10-30 min
Stage 3	Refractory SE: SE, that continues despite stage 1/2 treatment[1] subtle SE, stuporous SE	30-60 min
Stage 4	Super-refractory SE[2]: SE, that continues despite treatment with anaesthetics > 24 hours	>24h

1: Holtkamp *Lancet Neurol* 2007; 2: Shorvon and Trinka *Epilepsia* 2011;

Clinical course of convulsive status epilepticus

BUT: Most (17/29) RSE patients not in the ICU[4]

Refractory and Super-refractory SE represent 23%-43% of all status epilepticus[3,4,5]

Stage 3 — Refractory SE: SE, that continues despite stage 1/2 treatment[1]

subtle SE, stuporous SE

Stage 4 — Super-refractory SE[2]: SE, that continues despite treatment with anaesthetics > 24 hours

1: Holtkamp *Lancet Neurol* 2007; 2: Shorvon and Trinka *Epilepsia* 2011; 3: Mayer *Arch Neur* 2002, 4: Novy *Epilepsia* 2010, 5: Kellinghaus *Epil Behav* 2012

Etiology of refractory and super-refractory SE

	Refractory SE (n=29)	Non-Refractory SE (n=99)	p-value χ^2
Acute Symptomatic	19 (65.5%)	59 (59.6%)	0.667
Remote Symptomatic	5 (17.2%)	17 (17.2%)	
Progressive Symptomatic	4 (13.8%)	15 (15.2%)	
Cryptogenic	1 (3.4%)	8 (8.1%)	
Potentially fatal	**20 (69%)**	**45 (45.5%)**	**0.034**

Up to 50% without previous seizures

Novy et al. *Epilepsia* 2010

Contents lists available at ScienceDirect
Epilepsy & Behavior
journal homepage: www.elsevier.com/locate/yebeh

Preliminary results of the global audit of treatment of refractory status epilepticus

M. Ferlisi[a,1], S. Hocker[b,1], M. Grade[d], E. Trinka[c], S. Shorvon[d,*], on behalf of the International Steering Committee of the StEp Audit

International Steering Committee of the StEp Audit, Gagandeep Singh, Marko Ercegovac, Terry O'Brien, Mark Cook, Yasiri Zeid, Eva Kumlien, Uri Kramer, Reetta Kalvaiainen, Charles Newton, Rima Nabbout, Daniel Godoy, Stanislav Groppa, Eva Kumlien, Alla Guecht, Tony Wu

[a] Unit of Neurology "A", University Hospital of Verona, Italy
[b] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[c] Universitätsklinik für Neurologie, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria
[d] UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Causes of Super refractory SE

Fig. 1. Map of the countries where the cases have been reported.

- 488 cases from 44 countries
- **38% with Hx of epilepsy**
- First-line treatment was delayed and not in line with current guidelines
- midazolam (59%), followed by propofol and barbiturates
- **Seizure control in 74%**

Causes of status epilepticus and outcome.

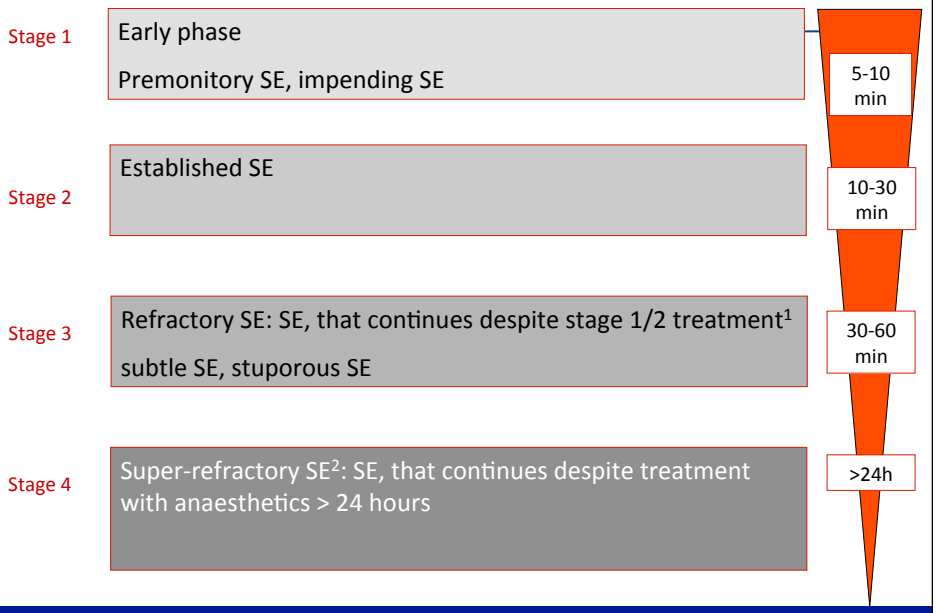
Cause	Recovered	Died/therapy withdrawn
Antiepileptic drug reduction/withdrawal	28 (90%)	3 (10%)
Genetic/chromosomal	6 (86%)	1 (14%)
Cerebral tumor	18 (82%)	4 (18%)
Unknown (cryptogenic)	63 (80%)	16 (20%)
Trauma	12 (80%)	3 (20%)
Mitochondrial disease	3 (75%)	1 (25%)
Vascular (including stroke)	42 (74%)	15 (26%)
Acute meningitis	8 (73%)	3 (27%)
Other infection	23 (72%)	9 (28%)
Alcohol	12 (67%)	6 (33%)
Other toxins	2 (67%)	1 (33%)
Immunological, all	17 (65%)	9 (35%)
Acute encephalitis	32 (65%)	17 (35%)
Metabolic	13 (62%)	8 (38%)
Anoxic (including cardiac arrest)	22 (49%)	23 (51%)

Ferlisi et al. Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.04.010

Agenda

- Definition and classification of status epilepticus
- Causes and mechanisms
- Staged Treatment approach
  - Refractory Status epilepticus
  - Super-refractory Status epilepticus
- Prognosis
- Concluding remarks

Clinical course of convulsive status epilepticus



1: Holtkamp *Lancet Neurol* 2007; 2: Shorvon and Trinka *Epilepsia* 2011;

	Diazepam	Lorazepam	Midazolam	Clonazepam
+	Rapid onset of action IV Rectal formulation available Long standing clinical experience in adults and children Widespread availability	Rapid onset of action IV Long lasting effect (>24h) after a single injection Long standing clinical experience Proven efficacy in randomised controlled trials in GCSE	Rapid onset of action with all routes Water solubility (IB, IN, IM) socially well accepted Lack of reactions at the infusion site Little risk of accumulation	Rapid onset of action IV Long lasting effect (>24h) after a single injection Long standing clinical experience
-	Short duration of action, due to rapid redistribution Accumulation with the risk of prolonged sedation and respiratory depression Adverse effects from the polypropylene solvent	Rapid development of tolerance Adverse effects from the polypropylene solvent	Short duration of action with risk of seizure relapse	-lack of RCTs Adverse effects from the polypropylene solvent

Mod. From: Trinka E and Brigo F , Benzodiazepines used primarily for emergency treatment. In: Treatment of Epilepsies, 5th Ed. Blackwell 2015

WHAT TO DO WHEN

A protocol for the inhospital emergency drug management of convulsive status epilepticus in adults

Stage I: Early Phase

Premonitory SE, impending SE

Shelley Jones,[1] Clemens Pahl,[2] Eugen Trinka,[3] Lina Nashef[4]

In-Hospital **Emergency** Drug Management of Convulsive Status Epilepticus in Adults
See page 2 for essential parallel general measures

STEP 1: benzodiazepine give if fitting for > 5 min

First choice:
Intravenous lorazepam; Usual dose bolus **2 to 4 mg** (maximum rate 2 mg/min). If necessary repeat up to a total maximum dose of 0.1 mg/kg.
OR Intravenous diazepam: Usual dose **5 to 10 mg** titrate for effect, up to 20 mg if necessary. Do not give too fast, to avoid respiratory depression (maximum rate 5 mg/min). Diazepam is rapidly redistributed and may accumulate with repeated dosing.
OR Intravenous clonazepam: Usual dose 1 mg, if necessary repeat 1 mg dose after 5 minutes (maximum rate 0.5 mg/min).
If intravenous is difficult or not possible:
- **Buccal midazolam:** Usual dose **10 mg** (Caution: Give 5 mg in the elderly or patients less than 50 kg). Repeat dose once after 10 minutes if necessary.[1] If buccal preparation not available, use 10 mg/2 mL injection via buccal route.

OR Intramuscular midazolam: Usual dose 10 mg (Caution: Give 5 mg in the elderly or patients weighing less than 50 kg). Repeat dose once after 10 minutes if necessary.
If intravenous, buccal and intramuscular are not possible:
- **Rectal diazepam:** Usual dose **10 mg** (caution: give 5 mg in elderly patients or patients weighing less than 50 kg). Repeat dose once after 10 minutes if necessary.

If seizures stop, the recurrence rate is high; most patients need an intravenous stage 2 anti-epileptic drug (see below for doses) to prevent further seizures

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Stage II: Established SE

STEP 2: If no response to step 1 WITHIN 10 min, give stage 2 agent and INFORM NEURO-INTENSIVIST or EXPERIENCED ANAESTHETIST

Second stage antiepileptic drug given **intravenously and inform neurointensivist or experienced anaesthetist**
See loading dose proformas for administration guidance

If there is no specific contraindication or a clear preference for alternative:
Phenytoin; **18 mg/kg** (range 15–20); **maximum rate 50 mg/min**. Infuse into large or central vein via filter with ECG and blood pressure monitoring (caution **hypotension, bradycardia)**. Check concomitant drugs (phenytoin is an enzyme inducer—its effect on the half-life of affected drugs is not immediate). For patients already on phenytoin, see note on page 2* before administering.
OR
Levetiracetam; 30 mg/kg (range 20–70); **infuse over 10 minutes**; no interactions; good side effect profile in this setting but comparative efficacy remains to be established; renal excretion.[2,3]
OR
Sodium Valproate; 30 mg/kg (range 15–30); **infuse over 5 minutes**
Contraindicated in mitochondrial disease. Avoid in status of unknown cause in young people. Caution: in pregnancy or acute liver failure, where an alternative is preferable. Check concomitant drugs (valproate is an enzyme inhibitor, with immediate effect on half-life of affected drugs).[4,5]
OR
Phenobarbital; 10 mg/kg (range 10–15)**; maximum rate 100 mg/min.** Monitor blood pressure, ECG and respiratory function (Caution: **respiratory depression** may occur—only give if ventilatory support can be provided). Check concomitant drugs (phenobarbital is an enzyme inducer—the effect of enzyme induction on half-life of affected drugs is not immediate).

ENSURE NEUROINTENSIVIST/EXPERIENCED ANAESTHETIST IS AWARE OF THE PATIENT
If seizures recur in patients who are haemodynamically stable, optimise dose of initial second stage intravenous antiepileptic drug and then consider another second stage intravenous antiepileptic drug.

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IV Lacosamide: safety studies

Open label multicentre trial
Patients with 1-2 AEDs (n=100, 16-60yrs)
IV loading with 200mg, 300mg, 400mg LCM over 15 min followed 12h later by PO LCM (50% of loading dose)

→400mg less well tolerated (TEAEs) than lower doses
→ small increase of PR from baseline at end of infusion (6.1, 8.6, 10.6ms)
→No prolongation of QTcF interval

Table 5. Summary of lacosamide plasma concentrations by dose group (pharmacokinetic set[a])

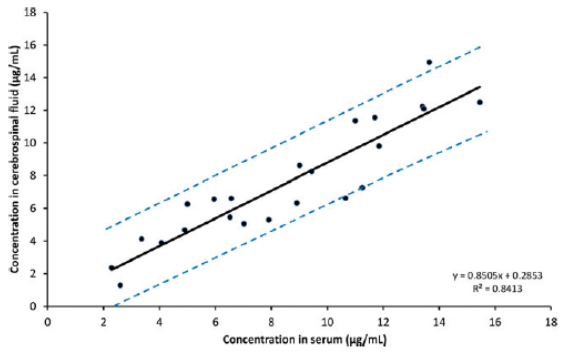
Assessment time	Statistics	LCM 200 mg n = 25	Combined LCM 300 mg[b] n = 50	LCM 400 mg n = 25
Day 1/End of infusion	n	23	45	23
	Mean (SD) (μg/ml)	6.586 (2.218)	9.319 (3.765)	12.330 (4.118)
	Min, Max (μg/ml)	3.193, 12.130	0.683, 16.017	4.779, 23.133
Day 1/Evening predose	n	23	40	19
	Mean (SD) (μg/ml)	2.927 (1.276)	3.243 (1.162)	4.500 (1.625)
	Min, Max (μg/ml)	1.612, 7.674	1.108, 8.154	2.843, 8.794
Day 2/Morning predose	n	20	45	21
	Mean (SD) (μg/ml)	3.379 (1.694)	3.844 (1.730)	4.917 (1.499)
	Min, Max (μg/ml)	1.794, 9.091	1.610, 11.067	3.384, 9.026

[a]Pharmacokinetic set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg LCM).

1: Fountain et al. Epilepsia 2012

CSF Concentration of Lacosamide

- 27 serum and cerebral spinal fluid (CSF) samples from 21 patients
- Lacosamide 50–600 mg/day over two or three doses
- 23 time-matched pairs of serum and CSF samples from 19 patients



Lacosamide concentration in CSF is approximately 85% of that found in serum

May et al. Epilepsia, 56(7):1134–1140, 2015

IV Lacosamide adverse events

- Studies for approval of LCM for treatment of painful neuropathy[2]
  → 1 report of atrial fibrillation correlate with LCM administration

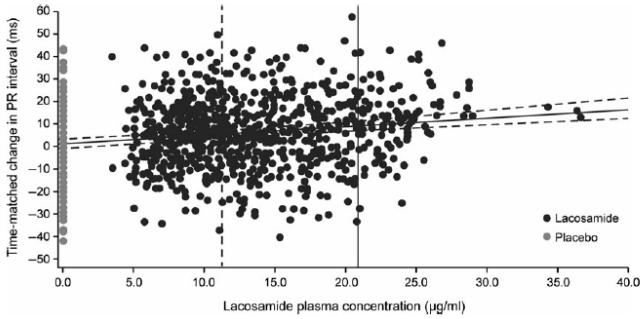
- 1 Case report[3] : 89-year-old woman –
  Medical history: heart failure, arterial hypertension, hypothyroidism

  NCSE: → LCM 400 mg within 6 hours
  Normal PQ interval before and after the first dose of LCM
  → reversible complete AV block approximately 30 minutes after the second bolus
  → caution when using high doses of LCM in patients with significant cardiac diseases

1: Biton et al. Epilepsia 2008; 2: DeGiorgio, Epilepsy Behav. 2010; 3: Krause et al., Epilepsy &Behaviour 2011;

Lacosamide cardiac safety: a thorough QT/QTc trial in healthy volunteers

LCM 400 mg/day (maximum-recommended daily dose, 6 days),
LCM 800 mg/day (supratherapeutic dose, 6 days),
PBOn (6 days)
Healthy volunteers



QTcI mean maximum difference from PBO was 4.3 ms and 6.3 ms for LCM 400 and 800 mg/day (90% confidence interval was below the 10 ms non-inferiority margin

Kropeit et al. Acta Neurol Scand 2015: DOI: 10.1111/ane.12416.

IV Lacosamide in Status Epilepticus[1-3]

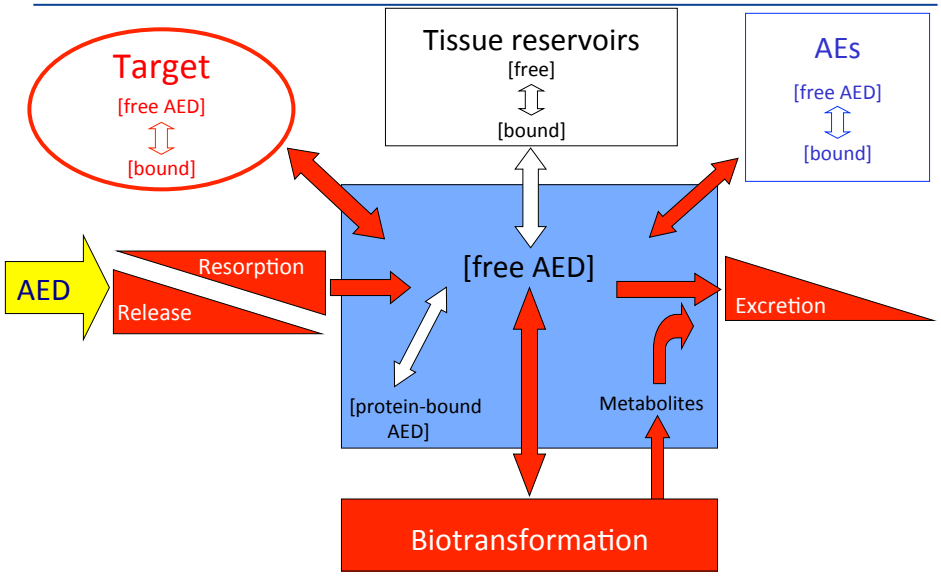
- [1-3]Overall **126 patients** with different types of SE treated with LCM
- Success rate 84/126: **66.7% [95%CI 58.4-74.9]**
- Most often used bolus: **400mg** (range 50-400mg)@ **40-80mg/min**
- No obvious CNS depressant effect, no hypotension, no ECG changes
- Angioedema (n=2), skin rash (n=1)

Open issues:

- Optimal bolus dose and rate not explored → satefty in high dose/high rate
- EEG response not well determined
- Clear order effect
- → Place in the treatment algorithm stage II or add on stage I
- **→ RCT is needed**

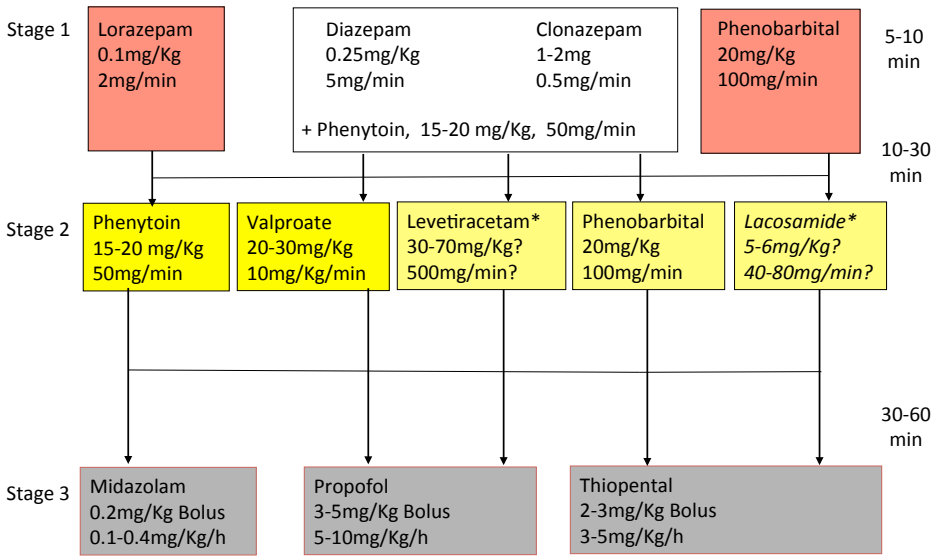
1: Höfler et al. Epilepsia 2011; 2: Trinka Epilepsia 2011; 3: Höfler and Trinka Epilepsia 2013

Interrelationship of absorption, distribution, binding, metabolism, and excretion of a drug



Modified after Buxton ILO. In Goodman and Gilman´s *The Pharmacological Basis of Therapeutics* 11th ed. 2006 p2

Staged approach to the treatment of focal NCSE without coma



Modified after: Trinka Nervenheilkunde 2007, Shorvon, Baulac, Cross, Trinka and Walker for the ILAE Task force on SE, Epilepsia 2008, Trinka E Klein Neurophysiologie 2012; Rosenow et al. Leitlinien der DGN, ÖGN, 2012

Stage III: Refractory SE

STEP 3:
If no response to step 2 within 30 minutes of onset anaesthesia and ICU admission

General anaesthesia with intubation and ventilation
Consider if haemodynamically unstable at any stage or if respiratory support is needed

- These drugs must be **administered by a neurointensivist/experienced anaesthetist in an intensive care unit (ICU) setting** as per local protocols to control clinical/EEG seizures
- *Induction* – usually propofol (1.5–3 mg/kg bolus) caution hypotension, bradycardia **OR**
  - thiopentone (usually 3–5 mg/kg bolus, additional boluses of 50 mg every 3 minutes until seizures terminated, may be given if blood pressure remains stable)
- *Maintenance* – Propofol 1–5 mg/kg/hour titrated to effect; prolonged use may lead to propofol infusion syndrome **OR**
  - midazolam if patient already ventilated, initial bolus 1 mg intravenously and titrate to effect then 0.05–0.20 mg/kg/hour titrated to effect **OR** consider propofol with midazolam **OR**
  - thiopentone 3–5 mg/kg/hour titrated to effect. Caution: hypotension, cardiac suppression, immunosuppression, hypokalaemia, pancreatitis and drug accumulation
- **EEG monitoring is indicated (continuous or minimum every 24 hours) to assess level of anaesthesia and abolition of ictal discharges.**

Over next 24-48 hours, optimise doses and levels of non-anaesthetic anti-epileptic drugs and, if no electrical or clinical evidence of ongoing seizures, withdraw anaesthesia to assess response.

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Anaesthetics: Overview

	BARB	PRO	MDZ
Mechanisms	$GABA_A$ (NMDA,Ca)	$GABA_A$ (NMDA?,Ca)	$GABA_A$
Loading dose	THP 2-7mg/kg PTB 5-15 mg/kg	2 mg/kg	0.1-0.3 mg/kg
Maintenance	THP 3-5 mg/kg/h PTB 1-5 mg/kg/h	2-5(10) mg/kg/h	0.05-0.6 mg/kg/h
Elimination $t_{1/2}$	THP 36h, PTB 22h	2h	0.5-50h
Disadvantages	Long wash-out	PRIS: check lactate, add BDZ	Increase dose with time

Kress 1987, Van Ness 1990, Parke 1992, Orser 1995, Cremer 2001, Zhan 2001, Claassen 2001 & 2002, Walder 2002, Vasile 2003, Charlesworth 2004, Marik 2004, Rogawsky 2004, Rossetti 2004, Parviainen 2006, Zarovnaya 2007, Iyer 2009

Practice Points

- Anesthetics should be initiated in
  - immediately refractory generalized convulsive SE (evolving to NCSE)
  - deferred in complex focal SE
  - never in absence SE
- Which is the preferred anesthetic?
  - Midazolam > Propofol >> Barbiturates
- How should anesthetics be used?
  - Target BS (1/10s) → 24h → weaning 12-14h → repeat
- Stop treatment?
  - only if evidence (!) that patient will not recover

Which Anaesthetic Drug?

There is no clear first choice....BUT....

Table 2 Outcome data

	Propofol	BBT	*P*
Patients	14	9	
Efficacy			
RSE controlled with first course of study drug	6 (43%)	2 (22%)	0.40
RSE treated subsequently	4/8 (50%)	5/7 (71%)	1.00
Functional outcome at 3 weeks (returned to baseline)	5 (36%)	3 (33%)	1.00
Functional outcome at 3 months (returned to baseline)	5 (36%)	4 (44%)	1.00
Mortality	6 (43%)	3 (33%)	1.00
Tolerability			
Thrombotic/embolic complication	0	0	1.00
Infections requiring antibiotics	7 (50%)	6 (66%)	0.67
Hypotension requiring specific treatment	7 (50%)	5 (55%)	1.00
Other severe complications	1 (7%)[a]	1 (11%)[b]	1.00
Study drug administration (days, median, range)	2.5 (0–7)	2 (0–4)	0.45
Intubation time in survivors (days, median, range)	4 (2–28)	13.5 (8–70)	0.03

Claassen et al. *Epilepsia* 2002, Rossetti et al. *Arch Neurol* 2005, Shorvon and Ferlisi *Brain* 2012; Rossetti et al. *Neurocrit Care* 2011

Anesthetic drugs in status epilepticus: Risk or rescue?

A 6-year cohort study

171 pts in ICUs 2005-2011, 37% with IV anaethetics

	Total cohort (n = 171)	Patients without IVADs (n = 108)	Patients with IVADs (n = 63)	*p* Value
Primary outcomes				
Seizure control, n (%)	162 (95)	105 (97)	57 (90)	<0.077[a]
Glasgow Outcome Scale score (GOS), n (%)				
GOS 1-3	117 (68)	68 (63)	49 (78)	0.044[c]
GOS>3	54 (32)	40 (37)	14 (22)	
Death, n (%)	30 (18)	11 (10)	19 (30)	<0.0001[c]
Secondary outcomes				
Duration of care, d, mean ± SD				
Hospital stay	22.4 ± 17.2	18.7 ± 13.7	28.9 ± 20.5	0.0005[b,c]
ICU stay	7.8 ± 9.0	4.5 ± 5.8	13.5 ± 10.7	<0.0001[b,c]
Discharge, n (%)				
Back home	35 (20)	28 (26)	7 (11)	0.030[a,c]
Rehabilitation	56 (33)	33 (31)	23 (37)	0.424
Other hospital (for palliative care)	37 (22)	29 (27)	8 (13)	0.035[a,c]
Nursing home (for palliative care)	13 (8)	7 (6)	6 (10)	0.553[a]

Sutter et al. *Neurology* 2014;82:656–664

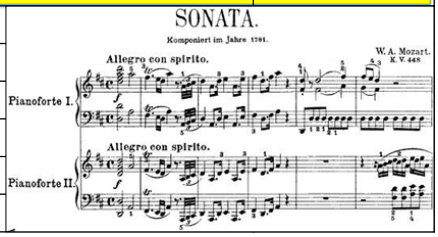
Super-refractory Status epilepticus

	Thiopental and pentobarbital (n=192)	Midazolam (n=585)	Propofol (n=143)
Control of SE	**64%**	**78%**	**68%**
No control ever achieved	5%	16%	11%
Breakthrough seizures	0%	3%	1%
Withdrawal seizures	9%	<1%	6%
Treatment failure because of side effects	3%	<1%	6%
Death during therapy	**19%**	**2%**	**8%**

Shorvon and Ferlisi Brain 2012

Super-refractory Status epilepticus

	Number of Publications	Patients
Ketamin	8	17
Inhalation narcotics	11	32
Hypothermia	5	10
Magnesium	3	11
Pyridoxin	5	14
Immunosuppressants/Steroids	15	50
Ketogenic diet	6	20
VNS		
DBS		
Epilepsy surgery		
ECT		
CSF drainage		
Mozart		



Shorvon and Ferlisi Brain 2011

Ketamine

- Ketamine (S-Ketamine) is a strong NMDA receptor antagonist; short t½ 1-2h
- 2 retrospective case series[1,2] and 9 single case reports[2], reporting 80 episodes of refractory status epilepticus in adults treated with ketamine:
- Largest series[2] with 46 adults and 12 children; 23 convulsive SE, 13 NCSE, 5 focal SE, 38 focal NCSE and 1 SE of infantile spasms
- The overall success rate was **56%**[2]
- Most often used bolus dose: ranging from **0.5 mg/kg to 2 mg/kg**, followed by infusion ranging from **0.6 mg/kg/h to maximal 10 mg/kg/h**
- Duration 2h to 140 days

1: Synowiec et al, Epilepsy Res 2013; 2: Gaspard et al, Epilepsia 2013; 3: Hsieh et al, Clin Neuropharmacol. 2010; 4: Ubogu et al, Epilepsy Behav. 2003; 5: Kramer et al, Neurocrit Care. 2012 ; 6: Kofke et al, J Neurosurg Anesthesiol. 1997; 6: Prüss et al, Epilepsy Res. 2008; 7: Robakis et al, Neurocrit Care. 2006; 8: Zeiler et al, Neurocrit Care 2014

Ketamine in RSE: The Salzburg Experience

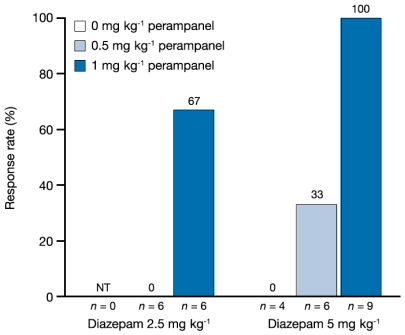
- 26/219 patients (64.5 years; range 15-80 at time of SE) with SE at the NICU
- **Causes**: 8 post-anoxic, 4 systemic infection, 4 stroke/intracerebral hemorrhage, 6 unknown, 4 pre-existing epilepsy with low AED level
- **Types of SE**: 2 myoclonic SE, 5 convulsive SE, 15 NCSE, 3 CSE→NCSE, 1 FSE

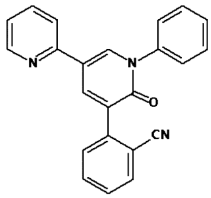
Patients	n = 26
Time of SE before KET	median 3.5 days (range 1-20)
Duration of KET treatment	median 5 days (range 1-16); 96 hours (range 8-355);
Dose of KET	median 1.91 mg/kg/h (range 0.11- 4.68); 150 mg/h (range 12.5-375)
Initial bolus of KET	6/26 patients, median 200 mg (range 200-300)
Initial continous infusion	20/26, median 200 mg/h (range 50-375)
Responder	**12/26 patients, 46%**
Mortality	**14/26 patients, 54% (due to underlying cause)**

Höfler et al. American Epilepsy Society Meeting, 2014

Perampanel in super refractory SE

- Perampanel (PER): non-competitive AMPA-antagonist;
- Lithium pilocarpine rat model of SE: efficacy of PER in termination of benzodiazepine resistant SE[4].
  - ED_{50} 1.7 mg/kg 10 minutes after SE onset; ED_{50} 5.1 mg/kg 30 min after SE onset; PER 8 mg/kg terminated SE in all rats at 10 and 30 min





PER and DZP were intravenously 30 min after seizure onset

4 Hanada et al. Pharmacol Res Perspect 2014

Perampanel in super refractory SE

Treatment	Time of treatment after seizure onset, min	Rats in which seizures were terminated, n/N	Efficacy at 30 min after treatment	Baseline	Before treatment	30 min after treatment
Diazepam						
20 mg kg⁻¹	10	2/6	+			
	30	0/6	–			
40 mg kg⁻¹	30	1/7	+			
			–			
Perampanel						
8 mg kg⁻¹	10	6/6	+			
	30	6/6	+			
GYKI52466						
50 mg kg⁻¹	30	2/4	+			
Diazepam plus perampanel						
Diazepam 5 mg kg⁻¹ Perampanel 1 mg kg⁻¹	30	9/9	+			

1 mV

4 Hanada et al. Pharmacol Res Perspect 2014

Perampanel in SRSE: The Salzburg Experience

Retrospective analysis (09/2012 - 01/2015); all in NICU

Twelve patients (75% women; median age 75 yrs [range 60-91]), with refractory and super-refractory SE received add on treatment with PER via nasogastric tube

SE type: NCSE with coma 5/12 (42%), NCSE without coma 6/12 (50%), focal motor 1/12(8 %)

Etiology:

acute symptomatic 5/12 (42%)

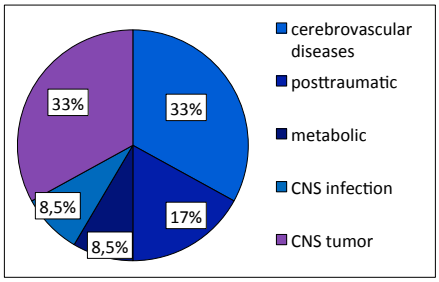
remote symptomatic 5/12 (42%)

progressive symptomatic 2/12 (16%)

SE de novo 7/12 (58%)

preexisting epilepsy 5/12

1/5 had insufficient AED levels



Rohracher A, et al, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.04.005

Perampanel in SRSE: The Salzburg Experience

AED treatment before PER:

	1st treatment	2nd treatment	3rd treatment	4th treatment	5th treatment	6th treatment	7th treatment
Lorazepam	11 (92%)	1 (8%)					
Midazolam	1 (8%)				1 (8%)		
Levetirazetam		9 (75%)	1 (8%)				
Phenytoin		2 (17%)	2 (17%)	3(25%)	1 (8%)		
Valproic acid			3 (25%)	3 (25%)			
Lacosamide			4 (33%)	1(8%)			
Topiramate				2 (17%)		2 (17%)	
Propofol					1 (8%)	1 (8%)	
Ketamine					1 (8%)	1 (8%)	
Carabamazepine							1 (8%)

83% concom EI (9/12 PHT, 1/10 CBZ)

Median number of prior AEDs: 4 [2 to 7], Median time to PER: 1.5 days [0.8 to 18.3]

Median initial dose PER: 4 mg [2 to 12], Median maximum dose PER: 12 mg [4 to 12]

Rohracher A, et al, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.04.005

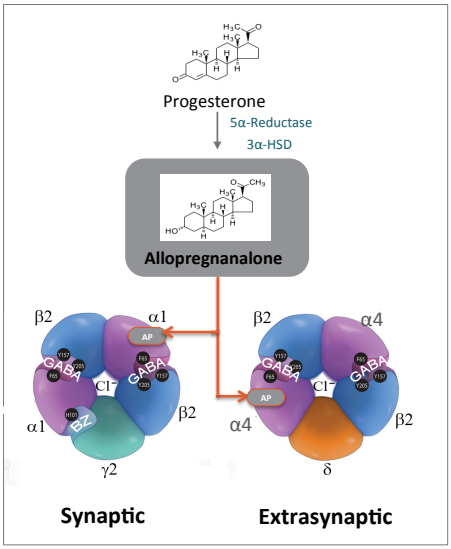
Perampanel in SRSE: The Salzburg Experience

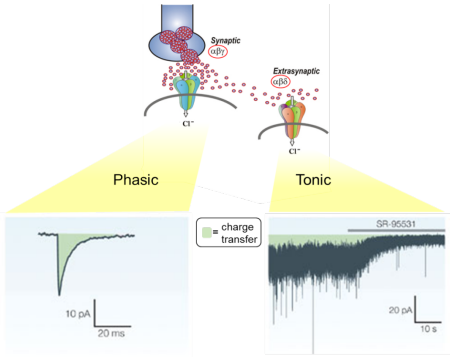
- STESS score positive (≥3 points) 8/12 pts (PPV 25%, NPV 75%)
- EMSE score positive (≥ 64 points) 8/12 pts (PPV 37.5%, NPV 100%)
- Outcome after SE (GOS):
  - good recovery 0/12 (0%), moderate disability 5/12 (42%), severe disability 2/12 (17%), persistent vegetative state 2/12 (17%), Dead 3/12 (25%)
- Median stay in the NICU 8 days [4 to 21]
- Median stay in hospital 18 days [6 to 70]
- No adverse effects regarding cardiorespiratory and laboratory parameters

→ Clinical and EEG improvement after PER in 2/12 pts. (17%)

Rohracher A, et al, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.04.005

Neurosteroids in Super-refractory SE



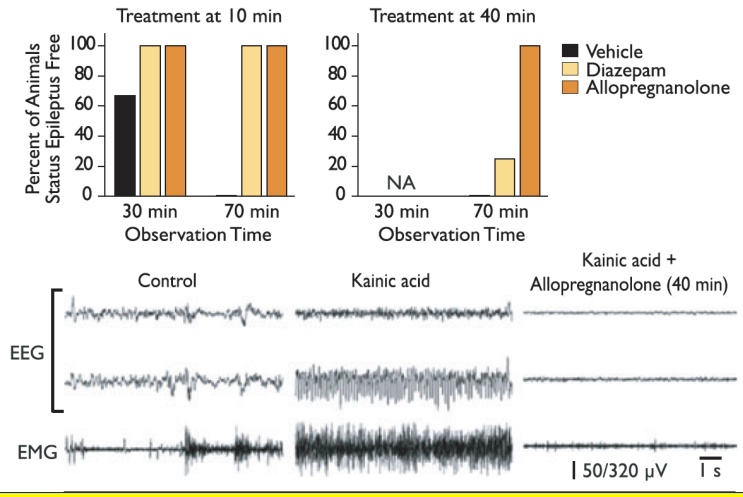


Neurosteroids modulate **synaptic** and **extrasynaptic** $GABA_A$ receptors

Benzodiazepines modulate only **synaptic** $GABA_A$ receptors

Rogawski et al. Epilepsia, 54(Suppl. 6):93–98, 2013

Neurosteroids in Super-refractory SE



Neurosteroids SGE-547 and SGE-102: in Phase II/III

1: Rogawski et al. Epilepsia, 54(Suppl. 6):93–98, 2013; 2: Reddy et al. Epilepsia, 54(Suppl. 6):81–83, 2013

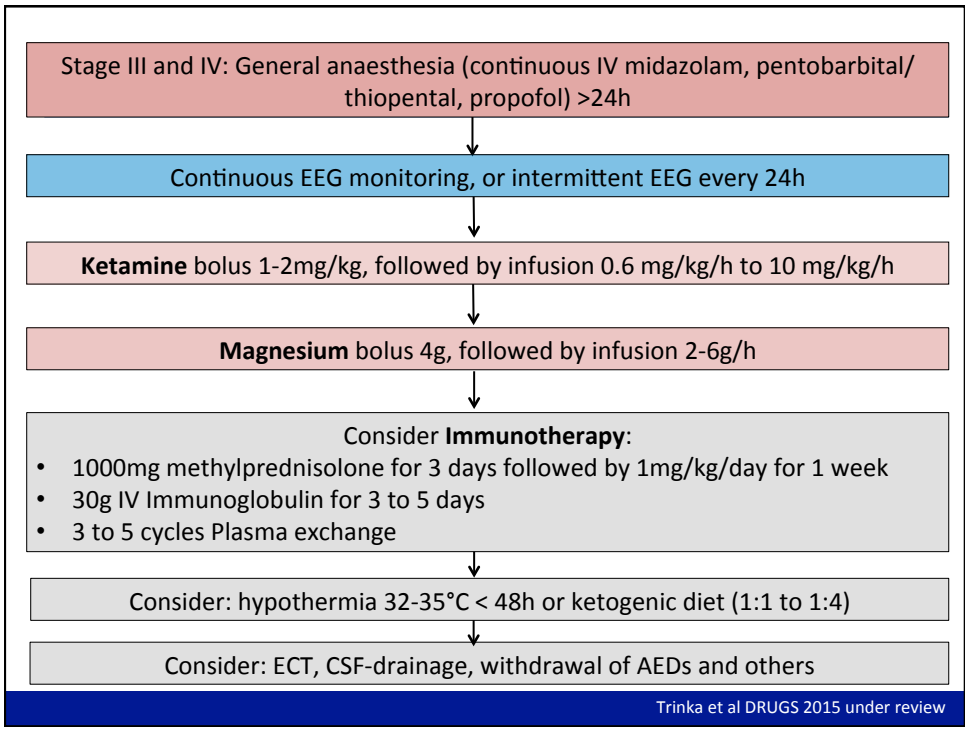
Ketogenic diet for adults in super-refractory status epilepticus

- Ten (4 woman) adult patients at 4 medical centers

median age was 33 years (IQR 21); 7 had encephalitis

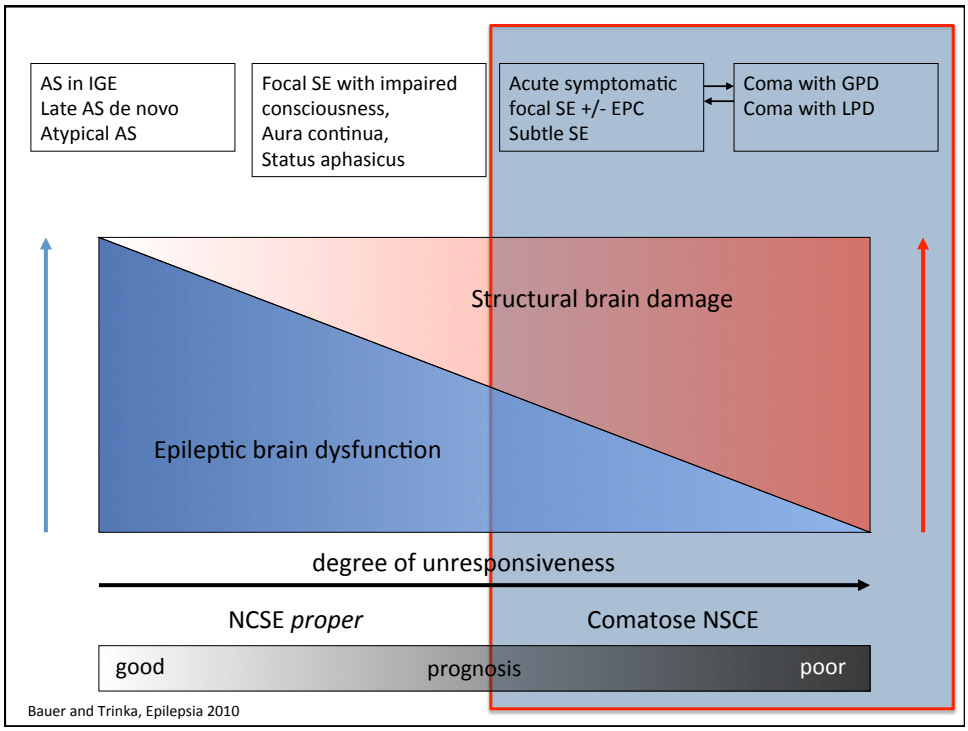
  - Median duration of SE before initiation of KD was 21.5 days (IQR 28)
  - Median number of antiepileptic medications used before initiation of KD was 7 (IQR 7)
  - Ninety percent of patients achieved ketosis
- **SE ceased in all patients achieving ketosis** in a median of 3 days (IQR 8)
- transient acidosis and hypertriglyceridemia and 2 patients ultimately died (unrelated to KD

Thakur et al. *Neurology* 2014;82:665–670



Agenda

- Definition and classification of status epilepticus
- Causes and mechanisms
- Staged Treatment approach
  - Refractory Status epilepticus
  - Super-refractory Status epilepticus
- Prognosis
- Concluding remarks



Bauer and Trinka, Epilepsia 2010

Is it comatose NCSE or coma?

1 Video was taped by Martin Soyer

Epilepsia, **(*):1–14, 2009
doi: 10.1111/j.1528-1167.2009.02297.x

CRITICAL REVIEW AND INVITED COMMENTARY

Nonconvulsive status epilepticus and coma

Gerhard Bauer and Eugen Trinka

Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Prevalence of NCSE in comatose patients[2] n=236

8% of all patients in coma without obvious clinical signs of SE

Age: 1 mo to 87 years

Persisting NCSE after "control" of GCSE[3] n=164

24h continuous EEG monitoring

48% with ictal EEG pattern: coma without obvious signs of SE

Consequently: There is no diagnosis of coma without EEG

1: Bauer and Trinka Epilepsia 2009; 2: Towne et al Neurology 2000; 3: DeLorenzo et al Epilepsia 1998

Era of Continuous Video EEG Monitoring

537 patients with suspected SE during three comparable 9-month period
2 groups before (groups 1 and 2) and 1 (group 3) after cont-video-EEG (cvEEG) introduction

Rate on NCSE diagnosis by group

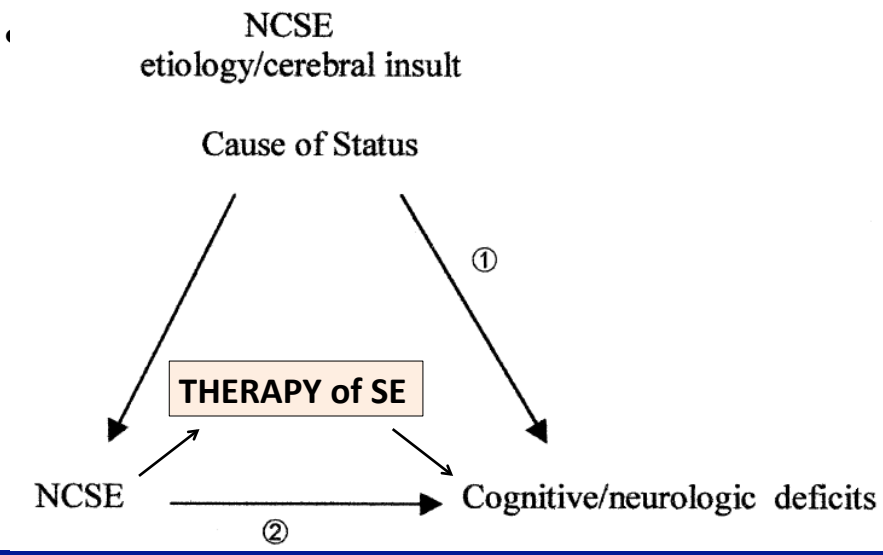
Group	Diagnosis rate	p
1	0.12 (16/129 of 754)	0.0546
2	0.14 (23/159 of 677)	
3	0.20 (49/249 of 682)	

Frequency of NCSE diagnosis increased significantly after implementation of cvEEG monitoring and was higher than the increment of performed investigations alone."

Sutter et al. *Epilepsia*, 52(3):453–457, 2011

No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: « The cure may be worse than the disease »)

P.W. Kaplan
Neurophysiol Clin 2000 ; 30 : 377-82



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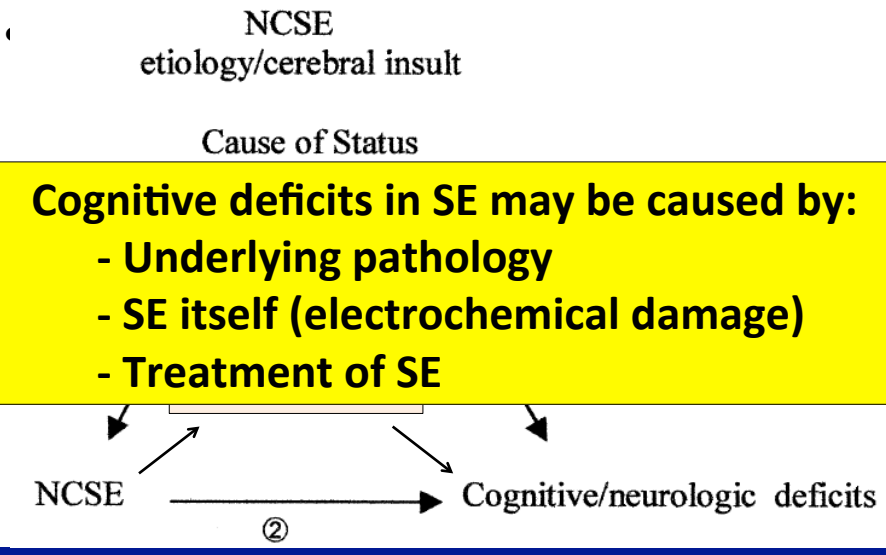


Status Epilepticus: Impact of Therapeutic Coma on Outcome*

Nicola A. Marchi, BM[1]; Jan Novy, MD[1]; Mohamed Faouzi, PhD[2]; Christine Stähli, RN[1]; Bernard Burnand, MD, MPH[2]; Andrea O. Rossetti, MD[1]

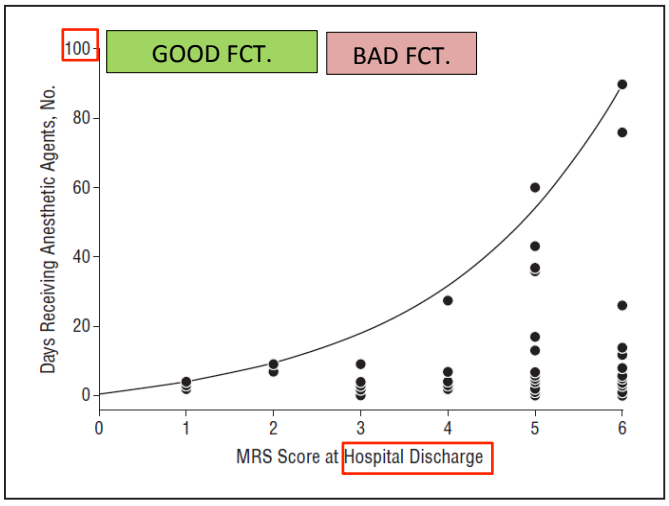
(*Crit Care Med* 2015; 43:1003–1009)

TABLE 4. Identified Variables Associated With Clinical Outcome in 467 Adults With Incident Status Epilepticus From the Fitted Multivariable Model

Variable	New Disability	Mortality
Age	**1.03 (1.01–1.05)**	**1.03 (1.01–1.05)**
Lack of previous seizures	**2.48 (1.49–4.15)**	1.35 (0.66–2.78)
Potentially fatal etiology	**2.72 (1.70–4.35)**	**7.2 (3.45–15.04)**
Status epilepticus severity score	1.12 (0.92–1.38)	**1.56 (1.17–2.10)**
Charlson Comorbidity Index	1.02 (0.92–1.13)	**1.18 (1.05–1.33)**

Statistical association does not always imply causal relationship

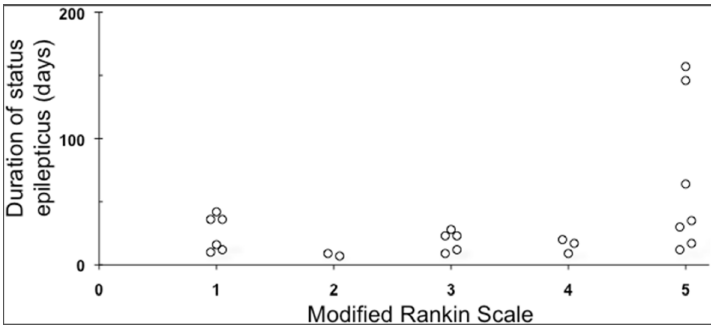
Outcome in refractory Status epilepticus: Time



Hocker et al. *JAMA Neurol* 2013; 70:72-77

Outcome in refractory Status epilepticus: Time

One year survivors



Retrospective;
19 centers: France
2001 – 2011;
polyvalent ICU
78 non-anoxic generalized convulsive refractory SE

Lai et al. *Crit Care* 2015; 19:199

Prognosis of Super refractory SE

Contents lists available at ScienceDirect
Epilepsy & Behavior
journal homepage: www.elsevier.com/locate/yebeh

Preliminary results of the global audit of treatment of refractory status epilepticus

M. Ferlisi[a,1], S. Hocker[b,1], M. Grade[d], E. Trinka[c], S. Shorvon[d,*], on behalf of the International Steering Committee of the StEp Audit

International Steering Committee of the StEp Audit, Gagandeep Singh, Marko Ercegovac, Terry O'Brien, Mark Cook, Yasiri Zeid, Eva Kumlien, Uri Kramer, Reetta Kalvaiainen, Charles Newton, Rima Nabbout, Daniel Godoy, Stanislav Groppa, Eva Kumlien, Alla Guecht, Tony Wu.

[a] Unit of Neurology "A", University Hospital of Verona, Italy
[b] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[c] Universitätsklinik für Neurologie, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria
[d] UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Fig. 1. Map of the countries where the cases have been reported.

- 488 cases from 44 countries
- **38% with Hx of epilepsy**
- First-line treatment was delayed and not in line with current guidelines
- midazolam (59%), followed by propofol and barbiturates
- **Seizure control in 74%**

36%

Neurological outcome of patients at the end of anesthesia.

mRS	N (%)
0 – No symptoms.	37 (9.4)
1 – No significant disability. Able to carry out all usual activities despite some symptoms.	43 (10.9)
2 – Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities.	25 (6.3)
3 – Moderate disability. Requires some help but able to walk unassisted.	37 (9.4)
4 – Moderately severe disability. Unable to attend to own bodily needs without assistance and unable to walk unassisted.	60 (15.2)
5 – Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	95 (24.1%)
6 – Dead.	97 (24.6)
Total	394 (100.0)

Ferlisi et al. Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.04.010

Group effects: duration

- Retrospective study from a developing country
- non-refractory SE (n=105), RSE (n=42), SRSE (n=30)

Variable	NRSE (*n*: 105)	RSE (*n*: 42)	SRSE (*n*: 30)
Age	33.8 ± 19.0	30.7 ± 14.8	24.6 ± 23.6
Children (< 16 yr)	20% (21/105)	9.5% (4/42)‡	53.3% (16/30)*
Female	39% (41/105)	35.7% (15/42)	56.7% (17/30)
History of epilepsy	41% (43/105)	35.7% (15/42)	16.7% (5/30)*
Acute symptomatic etiology	**56.2% (59/105)**	**69.0% (29/42)**	**80.0% (24/30)***
Known epileptics	0.9% (1/105)	0% (0/42)	0% (0/30)
Alcohol related	1.9% (2/105)	9.5% (4/42)	0% (0/30)
CNS vascular disease	18.1% (19/105)	14.2% (6/42)	3.3% (1/30)*
Metabolic	7.6% (8/105)	0% (0/42)	6.6% (2/30)
CNS tuberculosis	3.8% (4/105)	9.5% (4/42)	3.3% (1/30)
Neurocysticercosis	10.5% (11/105)	2.4% (1/42)	0% (0/30)
Presumed encephalitis	12.3% (13/105)‡	30.9% (13/42)‡	66.7% (20/30)*
Remote symptomatic etiology	**17.1% (19/105)**	**11.9% (6/42)**	**6.6% (3/30)**
Vascular	4.7% (5/105)	4.8% (2/42)	0.0% (0/30)
AED withdrawal	**18.1% (16/105)**	**9.5% (3/42)**	**13.3% (2/30)**
Idiopathic	0.9% (1/105)	0% (0/42)	0.0% (0/30)
Gliosis	0.9% (1/105)	0.0% (0/42)	0% (0/30)
GOS-good outcome	79% (83/105)†	57.1% (24/42)‡	33.3% (10/30)*
Death	6.7% (7/105)	35.7% (15/42)	40.0% (12/30)*

Good functional outcome decreases with refractoriness/duration of SE

Jalayakshmi et al. *Epilepsy Research* 2014; 108: 1609-1617

Group effects: neuroimaging

- Retrospective study from Italy
- SE (n=79) and functional outcome using mRS

Variable	mRS deterioration	No mRS deterioration	Total	*p*-value	Multivariate analysis[a]		
					OR	95% CI	*p*-value
SE on admission: yes/no	23/23	24/9	79	0.042	0.127	0.026–0.616	0.01
Age: median (range)	69 (18–89)	74 (40–90)	79	0.189			
Hospital stay duration:	22 (4–163)	14 (1–62)	79	0.004			
Tumor: yes/no	7/38	1/31	77	0.130			
Ischemic stroke: yes/no	5/40	2/30	77	0.693			
Remote lesions: yes/no	13/32	7/25	77	0.489			
Limbic encephalitis: yes/no	1/44	0/32	77	1.000			
Normal findings:	5/40	21/11	77	<0.001	0.031	0.006–0.155	<0.001

Higher rate of good functional outcome in patients with normal MRI, and SE on admission

Beluzzo et al. *Epilepsy Research* 2015; 110: 179-182

Scores for outcome prediction in SE

STESS[1]

Status Epilepticus Severity Score

- parameters (4):
  - aetiology
  - age
  - seizure type
  - level of consciousness before treatment
- score points:
  - a priori assumptions
- initial study
  - retrospective evaluation prospectively tested
- prospective validation: yes[3,4]

EMSE[2]

Epidemiology Based Mortality Score

- parameters (4):
  - aetiology
  - age
  - comorbidities
  - EEG
- score points:
  - epidemiological ("real world") data
- initial study
  - explorative, hypothesis generating
  - "fitting test/score to sample"
- prospective validation: *ongoing*

1: Rosetti et al. 2006; 2: Leitinger et al. Neurocritical Care 2015; 22: 273-282; 3: Rossetti et al. 2008; 4: Sutter et al. 2013

Status epilepticus severity score (STESS)[1,3,4]

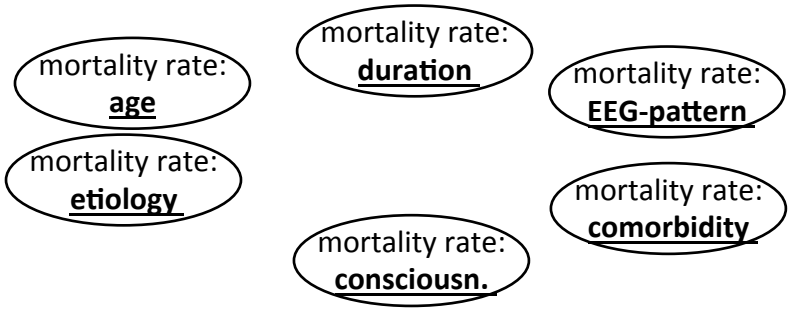
	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

Values of 3 or higher indicate high risk of death

1: Rosetti et al. 2006; 2: Leitinger et al. Neurocritical Care 2015; 22: 273-282; 3: Rossetti et al. 2008; 4: Sutter et al. 2013

Epidemiology Based Mortality Score in SE (EMSE)[1]

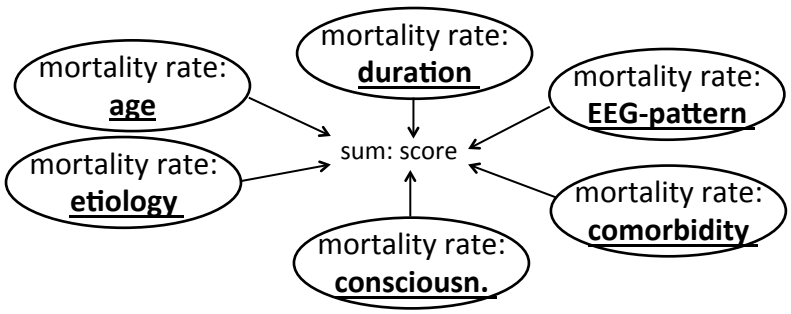
concept of EMSE:
✓ epidemiological studies present **mortality rates** for different parameters (e.g. age, aetiology,…)



1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

Epidemiology Based Mortality Score in SE (EMSE)[1]

concept of EMSE:
✓ epidemiological studies present **mortality rates** for different factors
✓ these mortality rates are taken as **points in a score** and summed up → those with many "risk points" should have a higher risk

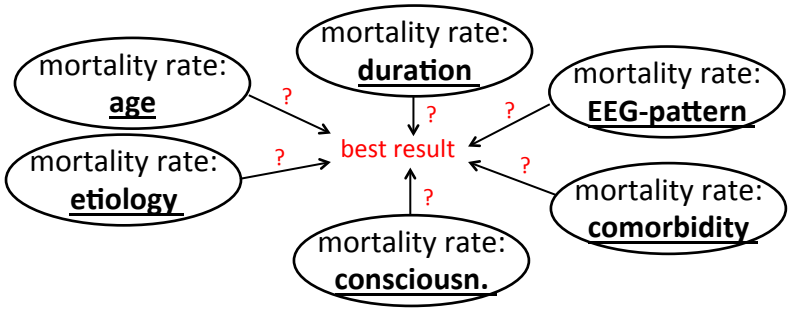


1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

Epidemiology Based Mortality Score in SE (EMSE)[1]

concept of EMSE:

- ✓ epidemiological studies present **mortality rates** for different factors
- ✓ these mortality rates are taken as **points in a score** and summed up → those with many "risk points" should have a higher risk
- ✓ test, which combination of factors yields best result



1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

Epidemiology Based Mortality Score in SE (EMSE)[1]

AETIOLOGY: score one stratum

aetiology E (reference: 1, 9)	EMSE-points
CNS-anomalies	2
drug reduction/ withdrawal, poor compliance	2
multiple sclerosis	5
remote cerebrovascular disease, brain injury	7
hydrocephalus	8
alcohol abuse	10
drug overdose	11
head trauma	12
cryptogenic	12
brain tumor	16
metabolic: sodium imbalance	17
metabolic disorders	22
acute cerebrovascular disease	26
CNS-infection: acute	33
anoxia	65

AGE: score one stratum

age A (reference: 11)	EMSE-points
21-30	1
31-40	2
41-50	3
51-60	5
61-70	7
71-80	8
>80	10

EEG: score only worst stratum

EEG E (reference 13, 14)	EMSE-points
burst suppression (spontaneous)	60
ASIDs	40
LPDs	40
GPDs	40
no LPDs, GPDs or ASIDs	0

COMORBIDITY: score each disease

comorbidity C (reference: 16)	EMSE-points
myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes	10
hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor including leukemia/ lymphoma	20
moderate or severe liver disease	30
metastatic solid tumor, AIDS	60

sum score = ___

1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

Epidemiology-Based Mortality Score in Status Epilepticus

Neurocrit Care (2015) 22:273–282

Table 3 Comparison of demographic and outcome data of studies with STESS and EMSE-score

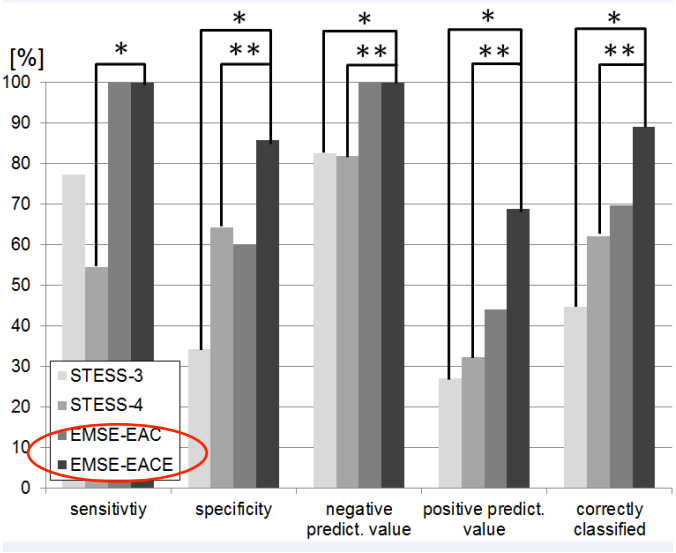
			N	≥ 65 a %	Without previous epilepsy		NCSE-C	STESS-3	NPV %	PPV %	CC %
STESS	Rossetti 2006[6]	ret	107	30	35	"cutoff 3"	##	STESS-3	96	25	
		pro	34	35	47			STESS-3	100	37.5	
	Rossetti 2008[8]	pro	154	#	48		12.3	STESS-3	97	39	
	Sutter 2013[9]	pro	171	56	54	"cutoff 4"	29	STESS-3	93	24	48.5
								STESS-4	91	36	73.1
EMSE		ret	92	62	50		18.5	STESS-3	82.8	27	44.6
								STESS-4	81.8	32.4	62
								EACE (all)	100	68.8	89.1
								($CONV_{only}$)	100	80.0	95.9

mean age of 57 a (121 survivors) versus 65 a (33 deceased)

NCSE-C reported together with GCSE in retro- (48 %) and prospective (47 %) part

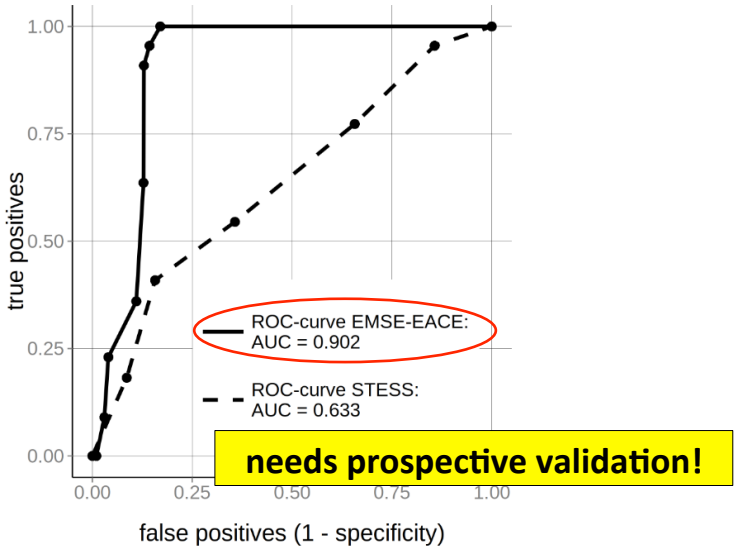
NCSE-C NCSE in coma, *ret* retrospective, *pro* prospective

EMSE vs. STESS: retrospective, explorative comparison



1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

EMSE vs. STESS: retrospective, explorative comparison



1: Leitinger et al. Neurocritical Care 2015; 22: 273-282;

Flexibility for global use

STESS[1]	EMSE[2]
Status Epilepticus Severity Score	**Epidemiology Based Mortality Score**
• prospective validation: yes[3,4]	• prospective validation: *ongoing*
• **developed countries**	• adaptable to each region in the world where epidemiological data are available

1: Rosetti et al. 2006; 2: Leitinger et al. Neurocritical Care 2015; 22: 273-282; 3: Rossetti et al. 2008; 4: Sutter et al. 2013

Premature mortality risk in people with convulsive epilepsy: Long follow-up of a cohort in rural China

*Ding Ding, †Wenzhi Wang, †Jianzhong Wu, ‡Hongchao Yang, ‡Shichuo Li, §Xiuying Dai, ¶Bin Yang, #Taiping Wang, **Chenglin Yuan, ††Guangyu Ma, ‡‡§§Gail S. Bell, ¶¶##Patrick Kwan, ***†††Hanneke M. de Boer, *Zhen Hong, and ‡‡§§***†††Josemir W. Sander

Epilepsia, 54(3):512–517, 2013

Burden, causes, and outcomes of people with epilepsy admitted to a rural hospital in Kenya

*†Symon M. Kariuki, *Eddie Chengo, *Fredrick Ibinda, *Rachael Odhiambo, *Anthony Etyang, *‡Anthony K. Ngugi, and *§Charles R. J. C. Newton

Epilepsia, **(*):1–8, 2015

Symon Kariuki

Clinical characteristics, etiology and long-term outcome of epilepsia partialis continua in adult patients in Thailand

Kanitpong Phabphal[a,*], Kitti Limapichat[a,1], Pornchai Sathirapanya[a,1], Suwanna Setthawatcharawanich[a,1], Alan Geater[b]

Epilepsy Research (2012) **100**, 179–187

Generalised convulsive status epilepticus in Singapore: Clinical outcomes and potential prognostic markers

Rahul Rathakrishnan[a,*], Novalia Purnama Sidik[b], Chan Yiong Huak[c], Einar P. Wilder-Smith[d]

Seizure 18 (2009) 202–205

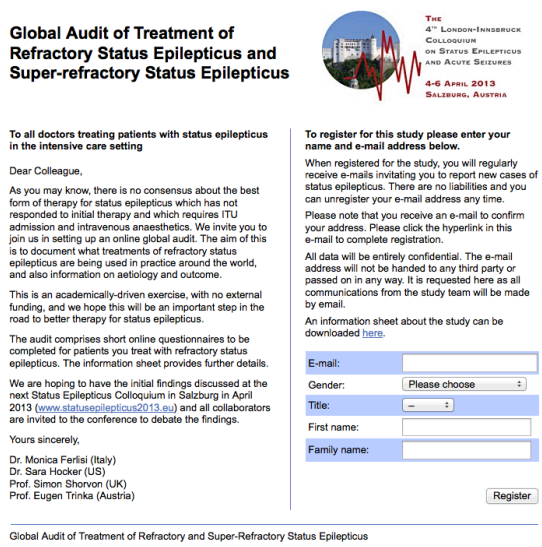
Adaptability for advances in treatment

STESS[1]	EMSE[2]
Status Epilepticus Severity Score	**Epidemiology Based Mortality Score**
• prospective validation: yes[3,4]	• prospective validation: *ongoing*
• **developed countries**	• adaptable to each region in the world where epidemiological data are available
• **adaptability to advances in medical therapy?**	• adaptability to advances in medical therapy: **yes!**

Optimal patient characterisation concerning outcome is mandatory to AVOID BIAS in interventional studies!

1: Rosetti et al. 2006; 2: Leitinger et al. Neurocritical Care 2015; 22: 273-282; 3: Rossetti et al. 2008; 4: Sutter et al. 2013

New initiative: www. Status-epilepticus.net



Global Audit of Treatment of Refractory Status Epilepticus and Super-refractory Status Epilepticus

The 4th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures
4-6 April 2013
Salzburg, Austria

To all doctors treating patients with status epilepticus in the intensive care setting

Dear Colleague,

As you may know, there is no consensus about the best form of therapy for status epilepticus which has not responded to initial therapy and which requires ITU admission and intravenous anaesthetics. We invite you to join us in setting up an online global audit. The aim of this is to document what treatments of refractory status epilepticus are being used in practice around the world, and also information on aetiology and outcome.

This is an academically-driven exercise, with no external funding, and we hope this will be an important step in the road to better therapy for status epilepticus.

The audit comprises short online questionnaires to be completed for patients you treat with refractory status epilepticus. The information sheet provides further details.

We are hoping to have the initial findings discussed at the next Status Epilepticus Colloquium in Salzburg in April 2013 (www.statusepilepticus2013.eu) and all collaborators are invited to the conference to debate the findings.

Yours sincerely,

Dr. Monica Ferlisi (Italy)
Dr. Sara Hocker (US)
Prof. Simon Shorvon (UK)
Prof. Eugen Trinka (Austria)

To register for this study please enter your name and e-mail address below.

When registered for the study, you will regularly receive e-mails invitating you to report new cases of status epilepticus. There are no liabilities and you can unregister your e-mail address any time.

Please note that you receive an e-mail to confirm your address. Please click the hyperlink in this e-mail to complete registration.

All data will be entirely confidential. The e-mail address will not be handed to any third party or passed on in any way. It is requested here as all communications from the study team will be made by email.

An information sheet about the study can be downloaded here.

E-mail:
Gender: Please choose
Title: –
First name:
Family name:
Register

Global Audit of Treatment of Refractory and Super-Refractory Status Epilepticus

Online audit of the treatments being used in status epilepticus around the world and their outcome

Short and easy to complete Questionnaires

!! PLEASE REGISTER AND TAKE PART !!

Conclusions

- SE is one of the most common neurological emergencies
- Establishment of a treatment protocol is of utmost importance → Dichotomy CSE vs. NCSE
- Prognostication with scores and EEG criteria for NCSE
- Lack of RCTs in stage 2, 3, and 4 → treatment decisions are based on
  - **co-morbidity etiology of SE, guidelines, ease of use, and doctor´s habits**
- **Stage 2: ESSET-Trial 2015: LEV vs. PHT vs. VPA**
- **Stage 3/4:** TRENdS Trial (LCM vs. PHT in NCSE): recruitment stopped
- **Stage 4:** Neurosteroids in Phase III development
- Antiglutamatergic drugs: KET, PER and other (BGG492, GYKI 52466 etc.) drugs on the horizon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